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(21) International Application Number: PCT/IB00/00366 (22) International Filing Date: 27 March 2000 (27.03.2000) (30) Priority Data: 60/132,130 30 April 1999 (30.04.1999) US (60) Parent Application or Grant PFIZER PRODUCTS INC. [/]; O. DOW, Robert, Lee [/]; O. LIU, Kevin, Kun-Chin [/]; O. MORGAN, Bradley, Paul [/]; O. SWICK, Andrew, Gordon [/]; O. DOW, Robert, Lee [/]; O. LIU, Kevin, Kun-Chin [/]; O. MORGAN, Bradley, Paul [/]; O. SWICK, Andrew, Gordon [/]; O. SPIEGEL, Allen, J. ; O.	Published	
(54) Title: GLUCOCORTICOID RECEPTOR MODULATORS (54) Titre: GLUCOCORTICOIDE RECEPTEUR MODULATEURS		
(57) Abstract <p>The present invention provides non-steroidal compounds of formula (I) which are selective modulators (i.e., agonists and antagonists) of a steroid receptor, specifically, the glucocorticoid receptor. The present invention also provides pharmaceutical compositions containing these compounds and methods for using these compounds to treat animals requiring glucocorticoid receptor agonist or antagonist therapy. Glucocorticoid receptor modulators are useful to treat diseases, such as obesity, diabetes, inflammation and others as described below. The present invention also provides intermediates and processes for preparing these compounds.</p> (57) Abrégé <p>L'invention porte sur des composés non stéroïdiens de formule (I) modulateurs sélectifs (c.-à-d. agonistes ou antagonistes) du récepteur des stéroïdes et en particulier du récepteur du glucocorticoïde. L'invention porte également sur des préparations pharmaceutiques contenant lesdits composés, et sur leurs procédés d'utilisation pour le traitement d'animaux nécessitant une thérapie par des agonistes ou antagonistes du récepteur du glucocorticoïde. Lesdits modulateurs peuvent servir à traiter des maladies telle que l'obésité, le diabète, les inflammations et autres, décrits ci-après. L'invention porte en outre sur des intermédiaires et procédés servant à la préparation de ces composés.</p>		

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<p>(21) International Application Number: PCT/IB00/00366 (22) International Filing Date: 27 March 2000 (27.03.00) (30) Priority Data: 60/132,130 30 April 1999 (30.04.99) US (71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton, CT 06340 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): DOW, Robert, Lee [US/US]; 132 Shore Road, Waterford, CT 06385 (US). LIU, Kevin, Kun-Chin [-/US]; 5 Goldfinch Terrace, East Lyme, CT 06333 (US). MORGAN, Bradley, Paul [US/US]; 84 Keeney Road, Lyme, CT 06371 (US). SWICK, Andrew, Gordon [US/US]; 19 Spring Rock Road, East Lyme, CT 06333 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.</p>
<p>(54) Title: GLUCOCORTICOID RECEPTOR MODULATORS</p> <div style="text-align: center;"> <p>(I)</p> </div> <p>(57) Abstract</p> <p>The present invention provides non-steroidal compounds of formula (I) which are selective modulators (i.e., agonists and antagonists) of a steroid receptor, specifically, the glucocorticoid receptor. The present invention also provides pharmaceutical compositions containing these compounds and methods for using these compounds to treat animals requiring glucocorticoid receptor agonist or antagonist therapy. Glucocorticoid receptor modulators are useful to treat diseases, such as obesity, diabetes, inflammation and others as described below. The present invention also provides intermediates and processes for preparing these compounds.</p>		

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Description

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GLUCOCORTICOID RECEPTOR MODULATORS

FIELD OF THE INVENTION

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The present invention provides non-steroidal compounds which are selective modulators (i.e., agonists and antagonists) of a steroid receptor, specifically, the glucocorticoid receptor. The present invention also provides pharmaceutical compositions containing these compounds and methods for using these compounds to treat animals requiring glucocorticoid receptor agonist and/or antagonist therapy. Glucocorticoid receptor modulators are useful to treat diseases, such as obesity, diabetes, inflammation and others as described below. The present invention also provides intermediates and processes for preparing these compounds.

BACKGROUND OF THE INVENTION

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Nuclear receptors are classically defined as a family of ligand dependent transcription factors, that are activated in response to ligand binding (R.M. Evans, 240 Science, 889 (1988)). Members of this family include the following receptors: glucocorticoid, mineralocorticoid, androgen, progesterone and estrogen. Naturally occurring ligands to these receptors are low molecular weight molecules that play an important role in health and in many diseases. Excesses or deficiencies of these ligands can have profound physiological consequences. As an example, glucocorticoid excess results in Cushing's Syndrome, while glucocorticoid insufficiency results in Addison's Disease.

The glucocorticoid receptor (GR) is present in glucocorticoid responsive cells where it resides in the cytosol in an inactive state until it is stimulated by an agonist. Upon stimulation the glucocorticoid receptor translocates to the cell nucleus where it specifically interacts with DNA and/or protein(s) and regulates transcription in a glucocorticoid responsive manner. Two examples of proteins that interact with the glucocorticoid receptor are the transcription factors, API and NFκ-B. Such interactions result in inhibition of API- and NFκ-B- mediated transcription and are believed to be responsible for some of the anti-inflammatory activity of endogenously administered glucocorticoids. In addition, glucocorticoids may also exert physiologic effects independent of nuclear transcription. Biologically relevant glucocorticoid receptor agonists include cortisol and corticosterone. Many synthetic glucocorticoid receptor agonists exist including dexamethasone, prednisone and prednisilone. By

5 definition, glucocorticoid receptor antagonists bind to the receptor and prevent
glucocorticoid receptor agonists from binding and eliciting GR mediated events,
10 including transcription. RU486 is an example of a non-selective glucocorticoid
receptor antagonist.

- 5 U.S. Patent No. 3,683,091 discloses phenanthrene compounds, specifically
certain di-7-hydroxy or methyl-2,3,4,4a,9,10-hexahydrophenanthren-2-one and 4a-
15 alkyl derivatives, hydrogenated derivatives, functional derivatives and optically active
isomers thereof useful as specific anti-acne agents.

- Japanese Patent Application, Publication No. 45014056, published 20 May
10 1970, discloses the manufacture of 1,2,3,4,9,10,11 α ,12-octahydro-7-methoxy-12 β -
20 butylphenanthren-2 β -ol and certain of its derivatives useful as antiandrogenic and
antianabolic drugs.

- Japanese Patent Application, Publication No. 6-263688, published 20
September 1994, discloses certain phenanthrene derivatives which are interleukin-1
25 15 (IL-1) inhibitors. It also discloses their preparation and certain intermediates thereto.
International Patent Application Publication No. WO 95/10266, published 20 April
1995, discloses the preparation and formulation of certain phenanthrene derivatives
as nitrogen monoxide synthesis inhibitors.

- Japanese Patent Application, Publication No. 45-36500, published 20
20 November 1970, discloses a method of making certain optically active phenanthrene
derivatives which are useful as antiandrogenic agents.

- European Patent Application, Publication No. 0 188 396, published 23 July
35 1986, discloses certain substituted steroid compounds, certain processes and
intermediates for preparing them, their use and pharmaceutical compositions
25 containing them. These compounds are disclosed to possess antiglucocorticoid
activity, and some of them have glucocorticoid activity.

- C.F. Bigge et al., J. Med. Chem. 1993, 36, 1977-1995, discloses the synthesis
and pharmacological evaluation of a series of octahydrophenanthrenamines and
40 certain of their heterocyclic analogues as potential noncompetitive antagonists of the
N-methyl-D-aspartate receptor complex.

- 45 P.R. Kanjilal et al., J. Org. Chem. 1985, 50, 857-863, discloses synthetic
studies toward the preparation of certain complex diterpenoids.

- G. Sinha et al., J. Chem. Soc., Perkin Trans. I (1983), (10), 2519-2528,
50 discloses the synthesis of the isomeric bridged diketones *cis*-3,4,4a,9,10,10a-

5 hexahydro-1,4a-ethanophenanthren-2(1*H*),12-dione and *trans*-3,4,4a,9,10,10a-
10 hexahydro-3,4a-ethanophenanthren-2(1*H*),12-dione by highly regioselective
intramolecular aldol condensations through the stereochemically defined *cis*- and
trans-2,2-ethylenedioxy-1,2,3,4,4a,9,10,10a-octahydrophenanthren-4a-
5 ylacetaldehydes.

U.R. Ghatak, M. Sarkar and S.K. Patra, Tetrahedron Letters No. 32, pp.
15 2929-2931, 1978, discloses a simple stereospecific route to certain polycyclic
bridged-ring intermediates useful in preparing some complex diterpenoids.

P.N. Chakraborty et al., Indian J. Chem. (1974), 12(9), 948-55, discloses the
10 synthesis of 1 α -methyl-1 β ,4a β -dicarboxy-1,2,3,4,4a,9,10,10a β -octahydro-
20 phenanthrene, an intermediate in the synthesis of certain diterpenoids and diterpene
alkaloids, and of 1 β ,4a β -dicarboxy-1,2,3,4,4a,9,10,10a α -octahydrophenanthrene.

E. Fujita et al., J. Chem. Soc., Perkin Trans. I (1974), (1), 165-77, discloses
25 the preparation of enmein from 5-methoxy-2-tetralone via ent-3- β ,2-epoxy-3-
15 methoxy-17-norkaurane-6 α ,16 α -diol.

H. Sdassi et al., Synthetic Communications, 25(17), 2569-2573 (1995)
discloses the enantioselective synthesis of (R)-(+)-4a-cyanomethyl-6-methoxy-
30 3,4,9,10-tetrahydrophenanthren-2-one, which is a key intermediate in morphinan
synthesis.

20 T. Ibuka et al., Yakugaku Zasshi (1967), 87(8), 1014-17, discloses certain
alkaloids of menispermaceous plants.

Japanese Patent 09052899, dated 25 February 1997, discloses certain
35 diterpene or triterpene derivatives which are leukotriene antagonists obtained by
extraction from *Tripterygium wilfordii* for therapeutic use.

25 U.S. Patent No. 5,696,127 discloses certain nonsteroidal compounds, such as
40 5H-chromeno[3,4-f]quinolines, which are selective modulators of steroid receptors.

U.S. Patent No. 5,767, 113 discloses certain synthetic steroid compounds
useful for concurrently activating glucocorticoid-induced response and reducing
multidrug resistance.

30 Published European Patent Application 0 683 172, published 11 November
1995, discloses certain 11,21-bisphenyl-19-norpregnane derivatives having anti-
glucocorticoid activity and which can be used to treat or prevent glucocorticoid-
dependent diseases.

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10 D. Bonnet-Delpon et al., Tetrahedron (1996), 52(1), 59-70, discloses certain CF_3 -substituted alkenes as good partners in Diels-Alder reactions with Danishefsky's diene and in 1,3-dipolar cycloadditions with certain nitrones and non-stabilized azomethine ylides.

15 5 International Patent Application Publication No. WO 98/26783, published 25 June 1998, discloses the use of certain steroid compounds with anti-glucocorticoid activity, with the exception of mifepristone, for preparing medicaments for the prevention or treatment of psychoses or addictive behavior.

20 10 International Patent Application Publication No. WO 98/27986, published 2 July 1998, discloses methods for treating non-insulin dependent Diabetes Mellitus (NIDDM), or Type II Diabetes, by administering a combination of treatment agents exhibiting glucocorticoid receptor type I agonist activity and glucocorticoid receptor type II antagonist activity. Treatment agents such as certain steroid compounds having both glucocorticoid receptor type I agonist activity and glucocorticoid receptor
25 15 type II antagonist activity are also disclosed.

30 International Patent Application Publication No. WO 98/31702, published 23 July 1998, discloses certain 16-hydroxy-11-(substituted phenyl)-estra-4,9-diene derivatives useful in the treatment or prophylaxis of glucocorticoid dependent diseases or symptoms.

35 20 Published European Patent Application 0 903 146, published 24 March 1999, discloses that the steroid 21-hydroxy-6,19-oxidoprogesterone (21OH- 6OP) has been found to be a selective antiglucocorticoid and is used for the treatment of diseases associated with an excess of glucocorticoids in the body, such as the Cushing's syndrome or depression.

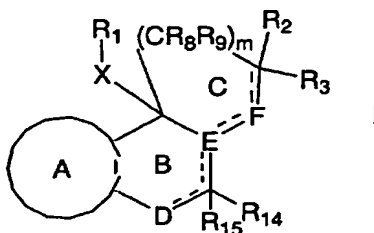
40 25 All of the above cited patents and published patent applications are hereby incorporated by reference herein in their entirety.

45 J. A. Findlay et al, Tetrahedron Letters No. 19, pp. 869-872, 1962, discloses certain intermediates in the synthesis of diterpene alkaloids.

50 30 Although there are glucocorticoid receptor therapies in the art, there is a continuing need for and a continuing search in this field of art for selective glucocorticoid receptor therapies. Thus, the identification of non-steroidal compounds which have specificity for one or more steroid receptors, but which have reduced or no cross-reactivity for other steroid or intracellular receptors, is of
55 significant value in this field.

SUMMARY OF THE INVENTION

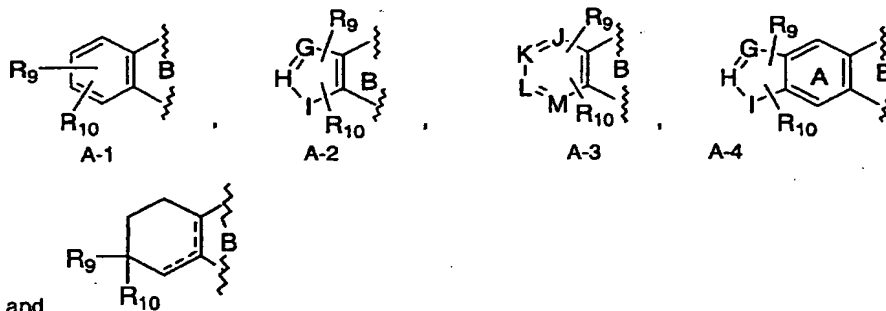
The present invention particularly provides:
compounds of formula I



isomers thereof, prodrugs of said compounds and isomers, and
pharmaceutically acceptable salts of said compounds, isomers and prodrugs;
wherein m is 1 or 2;

--- represents an optional bond;

A is selected from the group consisting of



and

A-5

D is CR₇, CR₇R₁₆, N, NR₇ or O;

E is C, CR₆ or N;

F is CR₄, CR₄R₅ or O;

G, H and I together with 2 carbon atoms from the A-ring or 2 carbon atoms
from the B-ring form a 5-membered heterocyclic ring comprising one or more N, O or

S atoms; provided that there is at most one of O and S per ring;

J, K, L and M together with 2 carbon atoms from the B-ring forms a 6-membered
heterocyclic ring comprising 1 or more N atoms;

X is a) absent, b) $-\text{CH}_2-$, c) $-\text{CH}(\text{OH})-$ or d) $-\text{C}(\text{O})-$;

R_1 is a) $-\text{H}$, b) $-\text{Z}-\text{CF}_3$, c) $-(\text{C}_1-\text{C}_6)\text{alkyl}$, d) $-(\text{C}_2-\text{C}_6)\text{alkenyl}$, e) $-(\text{C}_2-\text{C}_6)\text{alkynyl}$,
 f) $-\text{CHO}$, g) $-\text{CH}=\text{N}-\text{OR}_{12}$, h) $-\text{Z}-\text{C}(\text{O})\text{OR}_{12}$, i) $-\text{Z}-\text{C}(\text{O})-\text{NR}_{12}\text{R}_{13}$, j) $-\text{Z}-\text{C}(\text{O})-\text{NR}_{12}-\text{Z}-\text{het}$,
 k) $-\text{Z}-\text{NR}_{12}\text{R}_{13}$, l) $-\text{Z}-\text{NR}_{12}\text{het}$, m) $-\text{Z}-\text{het}$, n) $-\text{Z}-\text{O}-\text{het}$, o) $-\text{Z}-\text{aryl}'$, p) $-\text{Z}-\text{O}-\text{aryl}'$, q)
 5 $-\text{CHOH}-\text{aryl}'$ or r) $-\text{C}(\text{O})-\text{aryl}'$; wherein aryl' in substituents o) to r) is substituted
 independently with 0, 1 or 2 of the following: $-\text{Z}-\text{OH}$, $-\text{Z}-\text{NR}_{12}\text{R}_{13}$, $-\text{Z}-\text{NR}_{12}-\text{het}$,
 15 $-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$, $-\text{C}(\text{O})\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})-\text{het}$, $-\text{NR}_{12}-\text{C}(\text{O})-(\text{C}_1-\text{C}_6)\text{alkyl}$,
 $-\text{NR}_{12}-\text{C}(\text{O})-(\text{C}_2-\text{C}_6)\text{alkenyl}$, $-\text{NR}_{12}-\text{C}(\text{O})-(\text{C}_2-\text{C}_6)\text{alkynyl}$, $-\text{NR}_{12}-\text{C}(\text{O})-\text{Z}-\text{het}$, $-\text{CN}$,
 $-\text{Z}-\text{het}$, $-\text{O}-(\text{C}_1-\text{C}_3)\text{alkyl}-\text{C}(\text{O})-\text{NR}_{12}\text{R}_{13}$, $-\text{O}-(\text{C}_1-\text{C}_3)\text{alkyl}-\text{C}(\text{O})\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$,
 20 $-\text{NR}_{12}-\text{Z}-\text{C}(\text{O})\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, $-\text{N}(\text{Z}-\text{C}(\text{O})\text{O}(\text{C}_1-\text{C}_6)\text{alkyl})_2$, $-\text{NR}_{12}-\text{Z}-\text{C}(\text{O})-\text{NR}_{12}\text{R}_{13}$,
 $-\text{Z}-\text{NR}_{12}-\text{SO}_2\text{R}_{13}$, $-\text{NR}_{12}-\text{SO}_2-\text{het}$, $-\text{C}(\text{O})\text{H}$, $-\text{Z}-\text{NR}_{12}-\text{Z}-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$,
 $-\text{Z}-\text{NR}_{12}-\text{Z}-\text{NR}_{12}\text{R}_{13}$, $-\text{Z}-\text{NR}_{12}-(\text{C}_3-\text{C}_6)\text{cycloalkyl}$, $-\text{Z}-\text{N}(\text{Z}-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl})_2$, $-\text{SO}_2\text{R}_{12}$,
 $-\text{SO}_2\text{R}_{12}$, $-\text{SR}_{12}$, $-\text{SO}_2\text{NR}_{12}\text{R}_{13}$, $-\text{O}-\text{C}(\text{O})-(\text{C}_1-\text{C}_4)\text{alkyl}$, $-\text{O}-\text{SO}_2-(\text{C}_1-\text{C}_4)\text{alkyl}$, $-\text{halo}$ or
 $-\text{CF}_3$;

15 Z for each occurrence is independently a) $-(\text{C}_0-\text{C}_6)\text{alkyl}$, b) $-(\text{C}_2-\text{C}_6)\text{alkenyl}$ or
 c) $-(\text{C}_2-\text{C}_6)\text{alkynyl}$;

R_2 is a) $-\text{H}$, b) $-\text{halo}$, c) $-\text{OH}$, d) $-(\text{C}_1-\text{C}_6)\text{alkyl}$ substituted with 0 or 1 $-\text{OH}$, e)
 $-\text{NR}_{12}\text{R}_{13}$, f) $-\text{Z}-\text{C}(\text{O})\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, g) $-\text{Z}-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$, h) $-\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}$, i)
 30 $-\text{Z}-\text{O}-\text{C}(\text{O})-(\text{C}_1-\text{C}_6)\text{alkyl}$, j) $-\text{Z}-\text{O}-(\text{C}_1-\text{C}_3)\text{alkyl}-\text{C}(\text{O})-\text{NR}_{12}\text{R}_{13}$, k)
 20 $-\text{Z}-\text{O}-(\text{C}_1-\text{C}_3)\text{alkyl}-\text{C}(\text{O})-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, l) $-\text{O}-(\text{C}_2-\text{C}_6)\text{alkenyl}$, m) $-\text{O}-(\text{C}_2-\text{C}_6)\text{alkynyl}$, n)
 $-\text{O}-\text{Z}-\text{het}$, o) $-\text{COOH}$, p) $-\text{C}(\text{OH})\text{R}_{12}\text{R}_{13}$ or q) $-\text{Z}-\text{CN}$;

R_3 is a) $-\text{H}$, b) $-(\text{C}_1-\text{C}_{10})\text{alkyl}$ wherein 1 or 2 carbon atoms, other than the
 35 connecting carbon atom, may optionally be replaced with 1 or 2 heteroatoms
 independently selected from S, O and N and wherein each carbon atom is substituted
 25 with 0, 1 or 2 R_y , c) $-(\text{C}_2-\text{C}_{10})\text{alkenyl}$ substituted with 0, 1 or 2 R_y , d) $-(\text{C}_2-\text{C}_{10})\text{alkynyl}$
 wherein 1 carbon atom, other than the connecting carbon atom, may optionally be
 40 replaced with 1 oxygen atom and wherein each carbon atom is substituted with 0, 1
 or 2 R_y , e) $-\text{CH}=\text{C}=\text{CH}_2$, f) $-\text{CN}$, g) $-(\text{C}_3-\text{C}_6)\text{cycloalkyl}$, h) $-\text{Z}-\text{aryl}$, i) $-\text{Z}-\text{het}$, j)
 $-\text{C}(\text{O})\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, k) $-\text{O}(\text{C}_1-\text{C}_6)\text{alkyl}$, l) $-\text{Z}-\text{S}-\text{R}_{12}$, m) $-\text{Z}-\text{S}(\text{O})-\text{R}_{12}$, n) $-\text{Z}-\text{S}(\text{O})_2-\text{R}_{12}$, o)
 45 $-\text{CF}_3$, p) $-\text{NR}_{12}\text{O}-(\text{C}_1-\text{C}_6)\text{alkyl}$ or q) $-\text{CH}_2\text{OR}_y$.

provided that one of R_2 and R_3 is absent when there is a double bond
 between CR_2R_3 (the 7 position) and the F moiety (the 8 position) of the C-ring;

R_7 for each occurrence is independently a) -OH, b) -halo, c) -Z-CF₃, d) -Z-CF(C₁-C₃ alkyl)₂, e) -CN, f) -NR₁₂R₁₃, g) -(C₃-C₆)cycloalkyl, h) -(C₃-C₆)cycloalkenyl, i) -(C₀-C₃)alkyl-aryl, j) -het or k) -N₃;

or R_2 and R_3 are taken together to form a) =CHR₁₁, b) =NOR₁₁, c) =O, d) =N-NR₁₂, e) =N-NR₁₂-C(O)-R₁₂, f) oxiranyl or g) 1,3-dioxolan-4-yl;

R_4 and R_5 for each occurrence are independently a) -H, b) -CN, c) -(C₁-C₆)alkyl substituted with 0 to 3 halo, d) -(C₂-C₆)alkenyl substituted with 0 to 3 halo, e) -(C₂-C₆)alkynyl substituted with 0 to 3 halo, f) -O-(C₁-C₆)alkyl substituted with 0 to 3 halo, g) -O-(C₂-C₆)alkenyl substituted with 0 to 3 halo, h) -O-(C₂-C₆)alkynyl substituted with 0 to 3 halo, i) halo, j) -OH, k) (C₃-C₆)cycloalkyl or l) (C₃-C₆)cycloalkenyl;

or R_4 and R_5 are taken together to form =O;

R_6 is a) -H, b) -CN, c) -(C₁-C₆)alkyl substituted with 0 to 3 halo, d) -(C₂-C₆)alkenyl substituted with 0 to 3 halo, e) -(C₂-C₆)alkynyl substituted with 0 to 3 halo or f) -OH;

R_7 and R_{18} for each occurrence are independently a) -H, b) -halo, c) -CN, d) -(C₁-C₆)alkyl substituted with 0 to 3 halo, e) -(C₂-C₆)alkenyl substituted with 0 to 3 halo or f) -(C₂-C₆)alkynyl substituted with 0 to 3 halo; provided that R_7 is other than -CN or -halo when D is NR₇;

or R_7 and R_{18} are taken together to form =O;

R_8 , R_9 , R_{14} and R_{15} for each occurrence are independently a) -H, b) -halo, c) (C₁-C₆)alkyl substituted with 0 to 3 halo, d) -(C₂-C₆)alkenyl substituted with 0 to 3 halo, e) -(C₂-C₆)alkynyl substituted with 0 to 3 halo, f) -CN, g) -(C₃-C₆)cycloalkyl, h) -(C₃-C₆)cycloalkenyl, i) -OH, j) -O-(C₁-C₆)alkyl, k) -O-(C₁-C₆)alkenyl, l) -O-(C₁-C₆)alkynyl, m) -NR₁₂R₁₃, n) -C(O)OR₁₂ or o) -C(O)NR₁₂R₁₃;

or R_8 and R_9 are taken together on the C-ring to form =O; provided that when m is 2, only one set of R_8 and R_9 are taken together to form =O;

or R_{14} and R_{15} are taken together to form =O; provided that when R_{14} and R_{15} are taken together to form =O, D is other than CR₇ and E is other than C;

R_{10} is a) -(C₁-C₁₀)alkyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N₃, b) -(C₂-C₁₀)alkenyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N₃, c) -(C₂-C₁₀)alkynyl substituted with 0 to 3 substituents independently selected from -halo, -OH and -N₃, d) -halo, e) -Z-CN, f) -OH, g) -Z-het, h) -Z-NR₁₂R₁₃, i) -Z-C(O)-het, j)

-8-

- Z-C(O)-(C₁-C₆)alkyl, k) -Z-C(O)-NR₁₂R₁₃, l) -Z-C(O)-NR₁₂-Z-CN, m)
 -Z-C(O)-NR₁₂-Z-het, n) -Z-C(O)-NR₁₂-Z-aryl, o) -Z-C(O)-NR₁₂-Z-NR₁₂R₁₃, p)
 -Z-C(O)-NR₁₂-Z-O(C₁-C₆)alkyl, q) -(C₀-C₆)alkyl-C(O)OH, r) -Z-C(O)O(C₁-C₆)alkyl, s)
 -Z-O-(C₀-C₆)alkyl-het, t) -Z-O-(C₀-C₆)alkyl-aryl, u) -Z-O-(C₁-C₆)alkyl substituted with 0
 5 to 2 R_x, v) -Z-O-(C₁-C₆)alkyl-CH(O), w) -Z-O-(C₁-C₆)alkyl-NR₁₂-het, x)
 -Z-O-Z-het-Z-het, y) -Z-O-Z-het-Z-NR₁₂R₁₃, z) -Z-O-Z-het-C(O)-het, a1)
 -Z-O-Z-C(O)-het, b1) -Z-O-Z-C(O)-het-het, c1) -Z-O-Z-C(O)-(C₁-C₆)alkyl, d1)
 -Z-O-Z-C(S)-NR₁₂R₁₃, e1) -Z-O-Z-C(O)-NR₁₂R₁₃, f1)
 -Z-O-Z-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, g1) -Z-O-Z-C(O)-O(C₁-C₆)alkyl, h1)
 10 -Z-O-Z-C(O)-OH, i1) -Z-O-Z-C(O)-NR₁₂-O(C₁-C₆)alkyl, j1) -Z-O-Z-C(O)-NR₁₂-OH, k1)
 -Z-O-Z-C(O)-NR₁₂-Z-NR₁₂R₁₃, l1) -Z-O-Z-C(O)-NR₁₂-Z-het, m1)
 -Z-O-Z-C(O)-NR₁₂-SO₂-(C₁-C₆)alkyl, n1) -Z-O-Z-C(=NR₁₂)(NR₁₂R₁₃), o1)
 -Z-O-Z-C(=NOR₁₂)(NR₁₂R₁₃), p1) -Z-NR₁₂-C(O)-O-Z-NR₁₂R₁₃, q1) -Z-S-C(O)-NR₁₂R₁₃,
 r1) -Z-O-SO₂-(C₁-C₆)alkyl, s1) -Z-O-SO₂-aryl, t1) -Z-O-SO₂-NR₁₂R₁₃, u1)
 15 -Z-O-SO₂-CF₃, v1) -Z-NR₁₂C(O)OR₁₃ or w1) -Z-NR₁₂C(O)R₁₃;
 or R₉ and R₁₀ are taken together on the moiety of formula A-5 to form a) = O
 or b) = NOR₁₂;
 R₁₁ is a) -H, b) -(C₁-C₅)alkyl, c) -(C₃-C₆)cycloalkyl or d) -(C₀-C₃)alkyl-aryl;
 20 R₁₂ and R₁₃ for each occurrence are each independently a) -H, b)
 -(C₁-C₆)alkyl wherein 1 or 2 carbon atoms, other than the connecting carbon atom,
 may optionally be replaced with 1 or 2 heteroatoms independently selected from S, O
 and N and wherein each carbon atom is substituted with 0 to 6 halo, c)
 25 -(C₂-C₆)alkenyl substituted with 0 to 6 halo, or d) -(C₁-C₆)alkynyl wherein 1 carbon
 atom, other than the connecting carbon atom, may optionally be replaced with 1
 oxygen atom and wherein each carbon atom is substituted with 0 to 6 halo;
 or R₁₂ and R₁₃ are taken together with N to form het;
 30 or R₆ and R₁₄ or R₁₅ are taken together to form 1,3-dioxolanyl;
 aryl is a) phenyl substituted with 0 to 3 R_x, b) naphthyl substituted with 0 to 3
 R_x or c) biphenyl substituted with 0 to 3 R_x;
 35 het is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring
 containing from one (1) to three (3) heteroatoms independently selected from the
 group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in
 which any of the above heterocyclic rings is fused to a benzene ring or another
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heterocycle; and the nitrogen may be in the oxidized state giving the N-oxide form; and substituted with 0 to 3 R_x ;

R_x for each occurrence is independently a) -halo, b) -OH, c) $-(C_1-C_6)\text{alkyl}$, d) $-(C_2-C_6)\text{alkenyl}$, e) $-(C_2-C_6)\text{alkynyl}$, f) $-O(C_1-C_6)\text{alkyl}$, g) $-O(C_2-C_6)\text{alkenyl}$, h) $-O(C_2-C_6)\text{alkynyl}$, i) $-(C_6-C_6)\text{alkyl-NR}_{12}R_{13}$, j) $-C(O)-NR_{12}R_{13}$, k) $-Z-SO_2R_{12}$, l) $-Z-SOR_{12}$, m) $-Z-SR_{12}$, n) $-NR_{12}-SO_2R_{13}$, o) $-NR_{12}-C(O)-R_{13}$, p) $-NR_{12}-OR_{13}$, q) $-SO_2-NR_{12}R_{13}$, r) $-CN$, s) $-CF_3$, t) $-C(O)(C_1-C_6)\text{alkyl}$, u) $=O$, v) $-Z-SO_2\text{-phenyl}$ or w) $-Z-SO_2\text{-het'}$;

aryl' is phenyl, naphthyl or biphenyl;

het' is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring containing from one (1) to three (3) heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle;

provided that:

- 1) $X-R_1$ is other than hydrogen or methyl;
- 2) when R_9 and R_{10} are substituents on the A-ring, they are other than mono- or di-methoxy;
- 3) when R_2 and R_3 are taken together to form $=CHR_{11}$ or $=O$ wherein R_{11} is $-O(C_1-C_6)\text{alkyl}$, then $-X-R_1$ is other than $(C_1-C_4)\text{alkyl}$;
- 4) when R_2 and R_3 are taken together to form $=O$ and R_9 is hydrogen on the A-ring; or when R_2 is hydroxy, R_3 is hydrogen and R_9 is hydrogen on the A-ring, then R_{10} is other than $-O-(C_1-C_6)\text{alkyl}$ or $-O-CH_2\text{-phenyl}$ at the 2-position of the A-ring;
- 5) when $X-R_1$ is $(C_1-C_4)\text{alkyl}$, $(C_2-C_4)\text{alkenyl}$ or $(C_2-C_4)\text{alkynyl}$, R_9 and R_{10} are other than mono-hydroxy or $=O$, including the diol form thereof, when taken together;

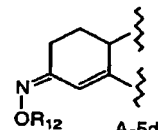
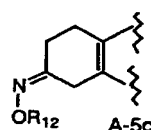
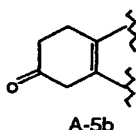
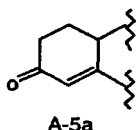
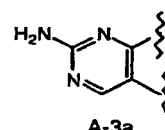
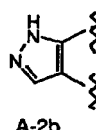
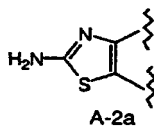
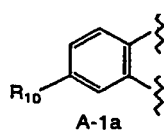
and

- 6) when X is absent, R_1 is other than a moiety containing a heteroatom selected from N, O or S directly attached to the juncture of the B-ring and the C-ring.

More particularly, the present invention provides:

compounds of formula I, isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs; wherein the A-ring is selected from the group consisting of:

-10-



D is CR₇, CR₇R₁₆ or O;

E is C, CR₆ or N;

5 F is CR₄, CR₄R₅ or O; and

X is -CH₂-.

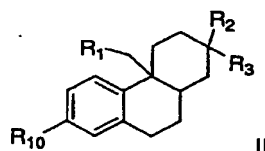
More particularly, the present invention provides:

compounds of formula I, isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;

10 wherein D is CH₂; E is CH; F is CH₂; R₈ is -H; R₉ is -H on the C-ring; m is 2; R₁₄ is -H; R₁₅ is -H; and the A-ring is the moiety of formula A-1a.

More particularly, the present invention provides:

compounds of formula II



15 isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;

wherein R₂ is a) -OH or b) -O-CH₂-het;

R₃ is a) -(C₁-C₆)alkyl substituted with 0 or 1 of the following: -CF₃, -CN,

45 -(C₃-C₆)cycloalkyl, -phenyl or -N₃, b) -C≡C- substituted with 1 of the following:

20 -(C₁-C₅)alkyl, -Cl, -CF₃, -(C₃-C₆)cycloalkyl, -phenyl or -benzyl; c) -CH₂OH, d)

-CH₂O(C₁-C₅)alkyl wherein 1 carbon atom may optionally be replaced with 1 oxygen atom,

e) -CH₂O(C₂-C₅)alkenyl, f) -CH₂O(C₂-C₅)alkynyl wherein 1 carbon atom may

50 optionally be replaced with 1 oxygen atom, g) -CH₂OR_y, h) -CN or i) -CF₃;

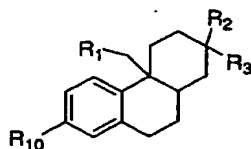
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R_7 is a) $-(C_1-C_3)\text{alkyl}-CF_3$, b) $-(C_3-C_6)\text{cycloalkyl}$, c) $-\text{phenyl}$ or d) $-\text{benzyl}$;
or R_2 and R_3 are taken together to form a) $-1,3\text{-dioxolan-4-yl}$ or b) $=\text{NOR}_{11}$;

R_{11} is a) $-\text{H}$, b) $-(C_1-C_5)\text{alkyl}$, c) $-(C_3-C_6)\text{cycloalkyl}$, d) $-\text{phenyl}$ or e) $-\text{benzyl}$.

In addition, more particularly, the present invention provides:

5 compounds of formula II



II

isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;

wherein R_1 is a) $-(C_1-C_4)\text{alkyl}$, b) $-(C_2-C_4)\text{alkenyl}$, c) $-\text{phenyl}$ substituted with 0 or 1 of the following: $-\text{OH}$, $-\text{NR}_{12}\text{R}_{13}$, $-\text{NR}_{12}\text{-C(O)-(C}_1\text{-C}_4\text{)alkyl}$, $-\text{CN}$, $-\text{Z-het}$, $-\text{O-(C}_1\text{-C}_3\text{)alkyl-C(O)-NR}_{12}\text{R}_{13}$, $-\text{NR}_{12}\text{-Z-C(O)-NR}_{12}\text{R}_{13}$, $-\text{Z-NR}_{12}\text{-SO}_2\text{-R}_{13}$, $-\text{NR}_{12}\text{-SO}_2\text{-het}$, $-\text{O-C(O)-(C}_1\text{-C}_4\text{)alkyl}$ or $-\text{O-SO}_2\text{(C}_1\text{-C}_4\text{)alkyl}$; d) $-\text{O-phenyl}$ substituted with 0 or 1 of the following: $-\text{Z-NR}_{12}\text{R}_{13}$ or $-\text{C(O)NR}_{12}\text{R}_{13}$, or e) $-\text{CH=CH-phenyl}$ wherein phenyl is substituted with 0 or 1 of the following: $-\text{Z-NR}_{12}\text{R}_{13}$ or $-\text{C(O)NR}_{12}\text{R}_{13}$;

15 Z for each occurrence is independently $-(C_0-C_2)\text{alkyl}$;

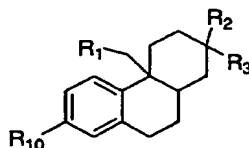
R_{10} is a) $-\text{CH(OH)(C}_1\text{-C}_5\text{)alkyl}$, b) $-\text{CN}$, c) $-\text{OH}$, d) $-\text{het}$, e) $-\text{C(O)-(C}_1\text{-C}_4\text{)alkyl}$, f) $-\text{C(O)-NR}_{12}\text{R}_{13}$, g) $-\text{C(O)-NH-Z-het}$, h) $-\text{O-(C}_0\text{-C}_2\text{)alkyl-het}$, i) $-\text{O-Z-C(O)-NR}_{12}\text{R}_{13}$, j) $-\text{O-Z-C(O)-NH-(C}_0\text{-C}_3\text{)alkyl-het}$ or k) $-\text{O-Z-C(O)-NH-(C}_0\text{-C}_3\text{)alkyl-NR}_{12}\text{R}_{13}$;

R_{12} and R_{13} are independently a) $-\text{H}$ or b) $-(C_1-C_4)\text{alkyl}$;

20 or R_{12} and R_{13} are taken together with N to form het.

Yet, even more particularly, the present invention provides:

compounds of formula II



II

25 isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;

wherein R_1 is a) $-(C_2-C_4)\text{alkyl}$, b) $-\text{CH}_2\text{-CH=CH}_2$ or c) $-\text{phenyl}$;

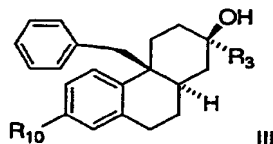
R_2 is -OH;

R_3 is a) $-(C_1-C_6)$ alkyl substituted with 0 or 1 CF_3 , b) $-C\equiv C-CH_3$, c) $-C\equiv C-Cl$, d) $-C\equiv C-CF_3$, e) $-CH_2O(C_1-C_3)$ alkyl substituted with 0 or 1 CF_3 , or f) $-CF_3$;

R_{10} is -OH.

Most particularly, the present invention provides:

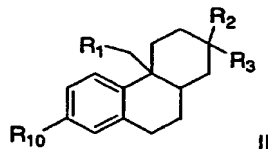
compounds of formula III



prodrugs thereof, or pharmaceutically acceptable salts of said compounds or prodrugs;

wherein R_3 and R_{10} are as defined immediately above.

In addition, the present invention more particularly provides:
compounds of formula II



isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;

wherein R_1 is a) $-(C_2-C_4)$ alkyl, b) $-CH_2-CH=CH_2$ or c) -phenyl;

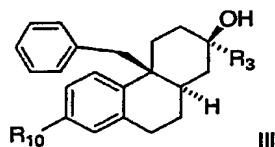
R_2 is -OH;

R_3 is a) $-(C_1-C_6)$ alkyl substituted with 0 or 1 CF_3 , b) $-C\equiv C-CH_3$, c) $-C\equiv C-Cl$, d) $-C\equiv C-CF_3$, e) $-CH_2O(C_1-C_3)$ alkyl substituted with 0 or 1 CF_3 , or f) $-CF_3$;

R_{10} is -CN.

Most particularly, the present invention provides:
compounds of formula III

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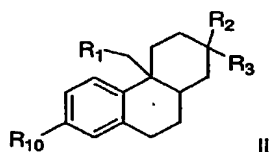


prodrugs thereof, or pharmaceutically acceptable salts of said compounds or prodrugs;

- wherein R_3 and R_{10} are as defined immediately above. Preferably, it provides a compound of formula III wherein R_3 is $-\text{C}\equiv\text{C}-\text{CH}_3$ and R_{10} is $-\text{CN}$; a compound of formula III wherein R_3 is $-(\text{CH}_2)_2-\text{CH}_3$ and R_{10} is $-\text{CN}$; a compound of formula III wherein R_3 is $-\text{CF}_3$ and R_{10} is $-\text{CN}$; and a compound of formula III wherein R_3 is $-\text{CH}_2\text{CH}_2\text{CF}_3$ and R_{10} is $-\text{CN}$; and pharmaceutically acceptable salts thereof.

In addition, the present invention more particularly provides:

- compounds of formula II



isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;

- wherein R_1 is a) $-(\text{C}_2-\text{C}_4)\text{alkyl}$, b) $-\text{CH}_2-\text{CH}=\text{CH}_2$ or c) $-\text{phenyl}$;

R_2 is $-\text{OH}$;

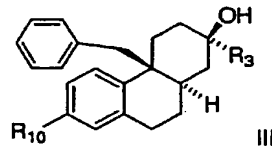
R_3 is a) $-(\text{C}_1-\text{C}_6)\text{alkyl}$ substituted with 0 or 1 CF_3 , b) $-\text{C}\equiv\text{C}-\text{CH}_3$, c) $-\text{C}\equiv\text{C}-\text{Cl}$, d) $-\text{C}\equiv\text{C}-\text{CF}_3$, e) $-\text{CH}_2\text{O}(\text{C}_1-\text{C}_3)\text{alkyl}$ substituted with 0 or 1 CF_3 , or f) $-\text{CF}_3$;

- R_{10} is $-\text{C}(\text{O})-\text{NH}-\text{Z}-\text{het}$ wherein het is selected from the group consisting of a) pyridinyl substituted with 0 or 1 methyl, b) pyrimidinyl, c) pyrazinyl, d) morpholinyl and e) oxadiazolyl;

Z is $-(\text{C}_0-\text{C}_2)\text{alkyl}$.

Most particularly, the present invention provides:
compounds of formula III

-14-

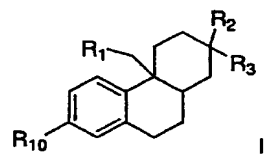


prodrugs thereof, or pharmaceutically acceptable salts of said compounds or prodrugs;

wherein R_3 is a) $-(CH_2)_2-CF_3$, b) $-(CH_2)_2-CH_3$, c) $-CH_3$, d) $-C\equiv C-CH_3$, e) $-C\equiv C-Cl$ or f) $-CF_3$;

R_{10} is as defined immediately above. Preferably, it provides a compound of formula III or a pharmaceutically acceptable salt thereof as follows: a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(4\text{-pyridinyl})$; a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2\text{-pyridinyl})$; a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(3\text{-pyridinyl})$; a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2\text{-methyl-3-pyridinyl})$; a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2\text{-methyl-3-pyridinyl})$; a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2\text{-pyridinyl})$; a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-C(O)-NH-CH_2-(2\text{-methyl-3-pyridinyl})$; a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2\text{-methyl-3-pyridinyl})$; a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-C(O)-NH-(3\text{-pyridinyl})$; and a compound of formula III wherein R_3 is $-CF_3$ and R_{10} is $-C(O)-NH-CH_2-(2\text{-methyl-3-pyridinyl})$.

In addition, the present invention more particularly provides: compounds of formula II



isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;

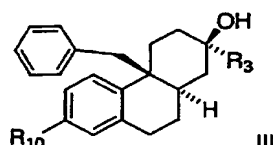
wherein R_1 is a) $-(C_2-C_4)\text{alkyl}$, b) $-\text{CH}_2\text{CH}=\text{CH}_2$ or c) $-\text{phenyl}$;

R_2 is $-\text{OH}$;

R_3 is a) $-(C_1-C_4)\text{alkyl}$ substituted with 0 or 1 CF_3 , b) $-\text{C}\equiv\text{C}-\text{CH}_3$, c) $-\text{C}\equiv\text{C}-\text{Cl}$, d) $-\text{C}\equiv\text{C}-\text{CF}_3$, e) $-\text{CH}_2\text{O}(C_1-C_3)\text{alkyl}$ substituted with 0 or 1 CF_3 , or f) $-\text{CF}_3$;

R_{10} is $-\text{O}(C_1-C_2)\text{alkyl-het}$ wherein het is selected from the group consisting of a) pyridinyl substituted with 0 or 1 methyl, b) pyrimidinyl, c) pyrazinyl, d) morpholinyl and f) oxadiazolyl.

Most particularly, the present invention provides:
compounds of formula III



prodrugs thereof, or pharmaceutically acceptable salts of said compounds or prodrugs;

wherein R_3 is a) $-(\text{CH}_2)_2-\text{CF}_3$, b) $-(\text{CH}_2)_2-\text{CH}_3$, c) $-\text{CH}_3$, d) $-\text{C}\equiv\text{C}-\text{CH}_3$, e) $-\text{C}\equiv\text{C}-\text{Cl}$ or f) $-\text{CF}_3$;

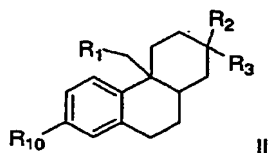
R_{10} is $-\text{O}(C_1-C_2)\text{alkyl-het}$ wherein het is selected from the group consisting of a) 2-pyridinyl, b) 3-pyridinyl, c) 4-pyridinyl, d) 2-methyl-3-pyridinyl and e) pyrazinyl.

Preferably, it provides a compound of formula III and pharmaceutically acceptable salts thereof as follows: a compound of formula III wherein R_3 is $-\text{C}\equiv\text{C}-\text{CH}_3$ and R_{10} is $-\text{O}-\text{CH}_2-(4\text{-pyridinyl})$; a compound of formula III wherein R_3 is $-\text{C}\equiv\text{C}-\text{CH}_3$ and R_{10} is $-\text{O}-\text{CH}_2-(2\text{-pyridinyl})$; a compound of formula III wherein R_3 is $-(\text{CH}_2)_2-\text{CF}_3$ and R_{10} is $-\text{O}-\text{CH}_2-(3\text{-pyridinyl})$; a compound of formula III

wherein R_3 is $-(\text{CH}_2)_2-\text{CF}_3$ and R_{10} is $-\text{O}-\text{CH}_2-(2\text{-methyl-3-pyridinyl})$; a compound of formula III wherein R_3 is $-(\text{CH}_2)_2-\text{CF}_3$ and R_{10} is $-\text{O}-\text{CH}_2-(2\text{-pyridinyl})$; and a compound of formula III wherein R_3 is $-\text{CF}_3$ and R_{10} is $-\text{O}-\text{CH}_2-(2\text{-methyl-3-pyridinyl})$.

In addition, the present invention more particularly provides:
compounds of formula II

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isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;
wherein R₁ is a) -(C₂-C₄)alkyl, b) -CH₂-CH=CH₂ or c) -phenyl;

R₂ is -OH;

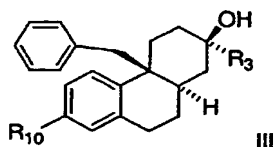
R₃ is a) -(C₁-C₄)alkyl substituted with 0 or 1 CF₃, b) -C≡C-CH₃, c) -C≡C-Cl, d) -C≡C-CF₃, e) -CH₂O(C₁-C₃)alkyl substituted with 0 or 1 CF₃, or f) -CF₃;

R₁₀ is a) -O-Z-C(O)-NH-(C₀-C₃)alkyl-N((C₁-C₂)alkyl)₂, b) -O-Z-C(O)-NR₁₂R₁₃, or c) -O-Z-C(O)-NH-(C₀-C₃)alkyl-het wherein het is selected from the group consisting of 1) pyridinyl substituted with 0 or 1 methyl, 2) pyrimidinyl, 3) pyrazinyl, 4) morpholinyl, 5) pyrrolidinyl, 6) imidazolyl and 7) oxadiazolyl;

R₁₂ and R₁₃ are independently a) -H or b) -(C₁-C₂)alkyl; or R₁₂ and R₁₃ are taken together with N to form pyrrolidinyl;

Z is -(C₀-C₁) alkyl.

Most particularly, the present invention provides:
compounds of formula III



prodrugs thereof, or pharmaceutically acceptable salts of said compounds or prodrugs;

wherein R₃ is a) -(CH₂)₂-CF₃, b) -(CH₂)₂-CH₃, c) -CH₃, d) -C≡C-CH₃, e) -C≡C-Cl or f) -CF₃;

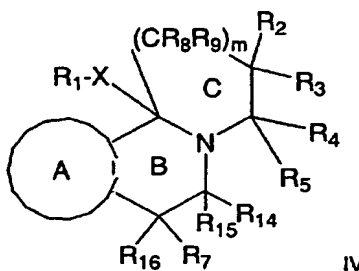
R₁₀ is a) -O-C(O)-NH-(C₀-C₃)alkyl-N((C₁-C₂)alkyl)₂, b) -O-C(O)-N(CH₃)₂, c) -O-C(O)-(1-pyrrolidinyl) or d) -O-C(O)-NH-(C₀-C₃)alkyl-het wherein het is selected from the group consisting of 1) 2-pyridinyl, 2) 3-pyridinyl, 3) 4-pyridinyl, 4)

2-methyl-3-pyridinyl, 5) pyrazinyl, 6) morpholinyl, 7) pyrrolidinyl and 8) imidazolyl.

Preferably, it provides a compound of formula III wherein R₃ is -C≡C-CH₃ and R₁₀ is -O-C(O)-NH-(CH₂)₂-(1-pyrrolidinyl); a compound of formula III wherein R₃ is -C≡C-CH₃

and R_{10} is $-O-C(O)-NH-(CH_2)_2-N(CH_3)_2$; a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-C(O)-NH-CH_2-2$ -pyridyl; a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-C(O)-NH-CH_2-4$ -pyridyl; and a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-C(O)-NH-CH_2-3$ -pyridyl; and pharmaceutically acceptable salts of the above compounds.

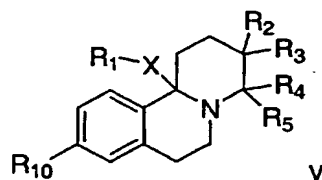
The present invention also provides:
compounds of formula IV



isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs; wherein the variables are as defined above for formula I.

More particularly, the present invention provides compounds of formula V, isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs; wherein R_8 is $-H$; R_9 is $-H$ on the C-ring; m is 2; R_7 is $-H$; R_{14} is $-H$; R_{15} is $-H$; R_{16} is $-H$; and the A-ring is the moiety of formula A-1a.

Even more particularly, the present invention provides compounds of formula V



isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically acceptable salts of said compounds, isomers or prodrugs;

wherein X is $-\text{CH}_2-$;

R_1 is a) $-(\text{C}_1-\text{C}_4)\text{alkyl}$, b) $-(\text{C}_2-\text{C}_4)\text{alkenyl}$, c) $-\text{phenyl}$ substituted with 0 or 1 of the following: $-\text{OH}$, $-\text{NR}_{12}\text{R}_{13}$, $-\text{NR}_{12}-\text{C}(\text{O})-(\text{C}_1-\text{C}_4)\text{alkyl}$, $-\text{CN}$, $-\text{Z-het}$, $-\text{O}-(\text{C}_1-\text{C}_3)\text{alkyl}-\text{C}(\text{O})-\text{NR}_{12}\text{R}_{13}$, $-\text{NR}_{12}-\text{Z}-\text{C}(\text{O})-\text{NR}_{12}\text{R}_{13}$, $-\text{Z}-\text{NR}_{12}-\text{SO}_2-\text{R}_{13}$, $-\text{NR}_{12}-\text{SO}_2-\text{het}$, $-\text{O}-\text{C}(\text{O})-(\text{C}_1-\text{C}_4)\text{alkyl}$ or $-\text{O}-\text{SO}_2-(\text{C}_1-\text{C}_4)\text{alkyl}$; d) $-\text{O-phenyl}$ substituted with 0 or 1 of the following: $-\text{Z}-\text{NR}_{12}\text{R}_{13}$ or $-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$; e) $-\text{CH}=\text{CH-phenyl}$ wherein phenyl is substituted with 0 or 1 of the following: $-\text{Z}-\text{NR}_{12}\text{R}_{13}$ or $-\text{C}(\text{O})\text{NR}_{12}\text{R}_{13}$;

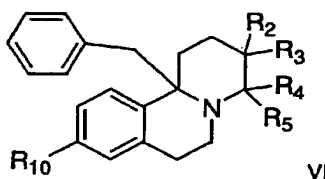
Z is for each occurrence independently $-(\text{C}_0-\text{C}_2)\text{alkyl}$;

R_4 and R_5 are each hydrogen or are taken together to form $=\text{O}$;

R_{10} is a) $-\text{CH}(\text{OH})(\text{C}_1-\text{C}_5)\text{alkyl}$, b) $-\text{CN}$, c) $-\text{OH}$, d) $-\text{het}$, e) $-\text{C}(\text{O})-(\text{C}_1-\text{C}_4)\text{alkyl}$, f) $-\text{C}(\text{O})-\text{NR}_{12}\text{R}_{13}$, g) $-\text{C}(\text{O})-\text{NH}-\text{Z-het}$, h) $-\text{O}-(\text{C}_0-\text{C}_2)\text{alkyl-het}$, i) $-\text{O}-\text{Z}-\text{C}(\text{O})-\text{NR}_{12}\text{R}_{13}$ or j) $-\text{O}-\text{Z}-\text{C}(\text{O})-\text{NH}-(\text{C}_0-\text{C}_3)\text{alkyl-het}$;

R_{12} and R_{13} for each occurrence are independently a) $-\text{H}$ or b) $-(\text{C}_1-\text{C}_4)\text{alkyl}$.

Most particularly, the present invention provides compounds of formula VI



isomers thereof, prodrugs of said compounds or isomers, or pharmaceutically

acceptable salts of said compounds, isomers or prodrugs;

wherein R_2 is a) $-\text{C}(\text{O})\text{OH}$, b) $-\text{C}(\text{O})\text{OCH}_3$, c) $-\text{C}(\text{O})\text{OCH}_2\text{CH}_3$ or d) $-\text{CH}_2\text{OH}$;

R_3 is a) $-(\text{CH}_2)_2-\text{CF}_3$, b) $-(\text{CH}_2)_2-\text{CH}_3$, c) $-\text{CH}_3$ or d) $-\text{CF}_3$;

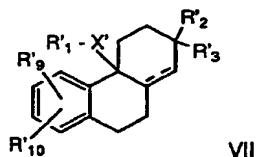
R_4 and R_5 are each hydrogen or are taken together to form $=\text{O}$;

R_{10} is a) $-\text{OH}$, b) $-\text{O}-(\text{C}_0-\text{C}_3)\text{alkyl-phenyl}$ or c) $-\text{O}-(\text{C}_0-\text{C}_3)\text{alkyl-het}$ wherein het is selected from the group consisting of a) 2-pyridinyl, b) 3-pyridyl, c) 4-pyridyl, d) 2-methyl-3-pyridyl and e) pyrazinyl.

The present invention also provides:

compounds of formula VII

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VII

and isomers thereof;

wherein - - - is an optional bond;

X' is -CH₂-;

R'₁ is phenyl substituted with 0, 1 or 2 R'_x;

R'₂ is -OH;

R'₃ is a) -(C₁-C₆)alkyl substituted with 0 or 1 R'_y or b) -(C₂-C₆)alkynyl substituted with 0 or 1 R'_y;

R'_y is -CF₃;

or R'₂ and R'₃ are taken together to form =O;

R'₉ is -H;

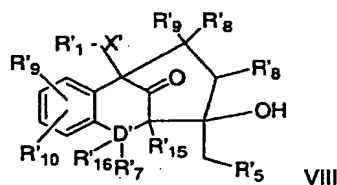
R'₁₀ is a) -halo, b) -C(O)OH, c) -C(O)O(C₁-C₆)alkyl, d) -C(O)-NR'₁₂R'₁₃, e) -CN, f) -OH or g) -O-(C₁-C₃)alkyl;

R'_x is a) -halo, b) -OH, c) -(C₁-C₆)alkyl, d) -CN, e) -CF₃, f)

-(C₀-C₆)alkyl-NR'₂R'₁₃, g) -C(O)-NR'₁₂R'₁₃, h) -NR'₁₂-SO₂R'₁₃, i) -NR'₁₂-C(O)-R'₁₃, j) -SO₂R'₁₂ or k) -SO₂-NR'₁₂R'₁₃;

R'₁₂ and R'₁₃ for each occurrence are each independently a) -H or b) -(C₁-C₆)alkyl. More particularly, the present invention provides the compound, 2(3H)-phenanthrenone, 4,4a,9,10-tetrahydro-7-bromo-4a-(phenylmethyl)-(S)-.

The present invention also provides:
compounds of formula VIII



VIII

and isomers thereof;

wherein D' is C;

X' is -CH₂-;

R'₁ is phenyl substituted with 0 to 2 R'_x;

$R'_5, R'_7, R'_8, R'_9, R'_{15}$ and R'_{16} for each occurrence are independently a) -H, b) -O-(C₁-C₆)alkyl, c) -(C₁-C₆)alkyl or d) halo;

R'_{10} is a) -halo, b) -CN, c) -OH, d) -C(O)-NR'₁₂R'₁₃, e) -C(O)-NR'₁₂Z'-het wherein het is substituted with 0 or 1 R'_x, f) -C(O)-NR'₁₂Z'-aryl wherein aryl is substituted with 0 or 1 R'_x, g) -O-(C₀-C₆)alkyl-het wherein het is substituted with 0 or 1 R'_x, or h) -O-(C₀-C₆)alkyl-aryl wherein aryl is substituted with 0 or 1 R'_x;

Z' is a) -(C₀-C₆)alkyl, b) -(C₂-C₆)alkenyl, or c) -(C₂-C₆)alkynyl;

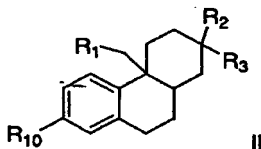
R'_x is a) -halo, b) -OH, c) -(C₁-C₆)alkyl, d) -CN, e) -CF₃, f) -(C₀-C₆)alkyl-NR'₁₂R'₁₃, g) -C(O)-NR'₁₂R'₁₃, h) -NR'₁₂-SO₂R'₁₃, i) -NR'₁₂-C(O)-R'₁₃, j) -SO₂R'₁₂ or k) -SO₂-NR'₁₂R'₁₃;

R'_{12} and R'_{13} for each occurrence are each independently a) -H or b) -(C₁-C₆)alkyl;

aryl is phenyl;

het is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring containing from one (1) to three (3) heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. More particularly, the present invention provides the compound, 1(R)-benzyl-6-methoxy-1-(S)-(3-oxo-butyl)-3,4-dihydro-1H-naphthalen-2-one.

In addition, the present invention provides compounds of formula II



an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

wherein R₁ is -phenyl;

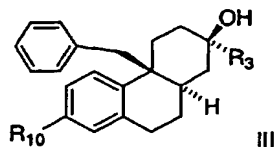
R₂ is -OH;

R₃ is a) -(C₁-C₆)alkyl substituted with 0 or 1 CF₃, b) -C≡C-CH₃, c) -C≡C-Cl, d) -C≡C-CF₃, e) -CH₂O(C₁-C₃)alkyl substituted with 0 or 1 CF₃, or f) -CF₃;

R₁₀ is -OH, -CN, -C(O)OH or -C(O)O(C₁-C₆)alkyl.

More particularly, the present invention provides compounds of formula III

-21-



a prodrug thereof, or a pharmaceutically acceptable salt of said compound or prodrug;

wherein R_3 is a) $-(CH_2)_2-CF_3$, b) $-(CH_2)_2-CH_3$, c) $-CH_3$, d) $-C\equiv C-CH_3$, e) $-C\equiv C-Cl$ or f) $-CF_3$; and

R_{10} is as defined immediately above. Most particularly, it provides a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-CF_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof; a compound of formula III wherein R_3 is $-CF_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof; and a compound of formula III wherein R_3 is $-CF_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof.

The present invention provides methods of treating obesity in a mammal comprising administering to said mammal a therapeutically effective amount of a

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compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug. More particularly, the present invention provides such methods wherein the mammal is a female or male human.

5 The present invention also provides pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent.

10 The present invention also provides pharmaceutical compositions for the treatment of obesity comprising an obesity treating amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent.

15 The present invention also provides pharmaceutical combination compositions comprising: a therapeutically effective amount of a composition comprising:

20 a first compound, said first compound being a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

25 a second compound, said second compound being a β_3 agonist, a thyromimetic agent, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutical carrier, vehicle or diluent. More particularly, it provides such compositions wherein the second compound is orlistat or sibutramine.

30 In addition, the present invention provides methods of treating obesity comprising administering to a mammal in need of such treatment

35 an amount of a first compound, said first compound being a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

40 a second compound, said second compound being a β_3 agonist, a thyromimetic agent, an eating behavior modifying agent or a NPY antagonist; and

45 wherein the amounts of the first and second compounds result in a therapeutic effect. More particularly, it provides such methods wherein the second compound is orlistat or sibutramine.

The present invention also provides kits comprising:

a) a first compound, said first compound being a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

b) a second compound, said second compound being a β_3 agonist, a thyromimetic agent, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

c) a container for containing said first and second dosage forms; wherein the amounts of said first and second compounds result in a therapeutic effect.

In addition, the present invention provides methods of inducing weight loss in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug. The present invention also provides pharmaceutical compositions for inducing weight loss comprising a weight loss-treating amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent.

Another aspect of the present invention provides methods of treating diabetes in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug.

The present invention also provides pharmaceutical compositions for the treatment of diabetes comprising a diabetes-treating amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent.

In addition, the present invention provides pharmaceutical combination compositions comprising: a therapeutically effective amount of a composition comprising:

a first compound, said first compound being a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin, troglitazone, sulfonylureas, glipizide, glyburide, or chlorpropamide; and

a pharmaceutical carrier, vehicle or diluent. More particularly, the present invention provides such pharmaceutical combination compositions wherein the aldose reductase inhibitor is 1-phthalazineacetic acid, 3,4-dihydro-4-oxo-3-[[5-trifluoromethyl)-2-benzothiazolyl]methyl]- or a pharmaceutically acceptable salt thereof.

The present invention also provides methods of treating diabetes comprising administering to a mammal in need of such treatment

an amount of a first compound, said first compound being a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin, troglitazone, sulfonylureas, glipizide, glyburide, or chlorpropamide; and

wherein the amounts of the first and second compounds result in a therapeutic effect.

In another aspect, the present invention provides pharmaceutical combination compositions comprising:

therapeutically effective amounts of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and

a compound selected from the group consisting of a glucocorticoid receptor agonist, a cholinomimetic drug, an anti-Parkinson's drug, an antianxiolytic drug, an antidepressant drug and an antipsychotic drug; and

a pharmaceutical carrier, vehicle or diluent. More particularly, it provides such compositions wherein the anti-Parkinson's drug is selected from the group consisting of L-dopa, bromocriptine and selegiline. More particularly, it provides such compositions wherein the antianxiolytic drug is selected from the group consisting of benzodiazepine, valium and librium. More particularly, it provides such compositions

wherein the antidepressant drug is selected from the group consisting of desipramine, sertraline hydrochloride and fluoxetine hydrochloride.

More particularly, it provides such compositions wherein the antipsychotic drug is selected from the group consisting of haloperidol and clozapine.

The present invention also provides kits comprising:

a) a first compound, said first compound being a compound of formula I, an isomer thereof, a prodrug said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

b) a second compound, said second compound being selected from the group consisting of a glucocorticoid receptor agonist; a cholinomimetic drug; an anti-Parkinson's drug; an anxiolytic drug; an antidepressant drug; and an antipsychotic drug; and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

c) a container for containing said first and second dosage forms wherein the amounts of said first and second compounds result in a therapeutic effect. More particularly, it provides such kits wherein the anti-Parkinson's drug is selected from the group consisting of L-dopa, bromocriptine and selegiline. More particularly, it provides such kits wherein the anxiolytic drug is selected from the group consisting of benzodiazepine, valium and librium. More particularly, it provides such kits wherein the antidepressant drug is selected from the group consisting of desipramine, sertraline hydrochloride and fluoxetine hydrochloride. More particularly, it provides such kits wherein the antipsychotic drug is selected from the group consisting of haloperidol and clozapine.

In another aspect, the present invention provides methods of treating anxiety in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug. It also provides pharmaceutical compositions for the treatment of anxiety comprising an anxiety-treating amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent.

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In another aspect, the present invention provides methods of treating depression in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug. It also provides pharmaceutical compositions for the treatment of depression comprising a depression-treating amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent.

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In another aspect, the present invention provides methods of treating neurodegeneration in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug. It also provides pharmaceutical compositions for the treatment of neurodegeneration comprising a neurodegeneration-treating amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent.

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In other aspects, the present invention provides the following methods:
20 methods of affecting glucocorticoid receptor activity comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; methods of modulating a process mediated by glucocorticoid receptor comprising administering to a mammal in need thereof a therapeutically effective amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; methods of treating a mammal requiring glucocorticoid receptor therapy comprising administering to said mammal a therapeutically effective amount of a glucocorticoid receptor modulator compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug.

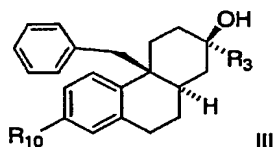
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In another aspect, the present invention provides methods of treating an inflammatory disease in a mammal comprising administering to said mammal a therapeutically effective amount of a compound of formula I, an isomer thereof, a

prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug. More particularly, it provides such methods wherein the mammal is a female or male human.

The present invention also provides pharmaceutical compositions for the treatment of an inflammatory disease comprising an inflammatory-treating amount of a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier.

In another aspect, the present invention provides methods for the treatment of an inflammatory disease in a mammal which comprises: administering to said mammal therapeutically effective amounts of a glucocorticoid receptor modulator and a glucocorticoid receptor agonist. More particularly, it provides such methods which further comprise reducing the undesirable side effects of said treatment. Also, it provides such methods wherein the inflammatory disease is selected from the group consisting of arthritis, asthma, rhinitis and immunomodulation. More particularly, it provides such methods wherein the glucocorticoid receptor modulator is a compound of formula I, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug. Also, more particularly, it provides such methods wherein the glucocorticoid receptor agonist is a compound selected from the group consisting of prednisone, prednylidene, prednisolone, cortisone, dexamethasone and hydrocortisone.

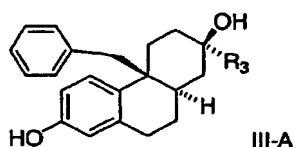
The present invention also provides a process for preparing a compound of formula III



wherein R_3 is a) $-(CH_2)_2-CF_3$, b) $-(CH_2)_2-CH_3$, c) $-CH_3$, d) $-C\equiv C-CH_3$, e) $-C\equiv C-Cl$ or f) $-CF_3$; and R_{10} is $-O-CH_2-het$ wherein het is pyridinyl substituted with 0 or 1 methyl;

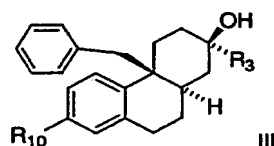
which comprises reacting a compound of formula III-A

-28-



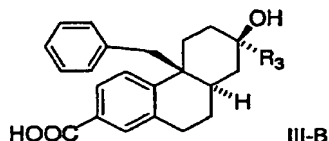
wherein R_3 is as defined above, with a base in an aprotic solvent at room temperature to 200°C; and then with a compound of formula $R_{10}-X_1$ wherein R_{10} is as defined above and $-X_1$ is halo, mesylate or tosylate. More particularly, it provides this process wherein the base is NaH, *t*-butoxide or Et_3N ; and the solvent is DMF or THF.

The present invention also provides a process for the preparing a compound of formula III



wherein R_3 is a) $-(CH_2)_2-CF_3$, b) $-(CH_2)_2-CH_3$, c) $-CH_3$, d) $-C\equiv C-CH_3$, e) $-C\equiv C-Cl$ or f) $-CF_3$; R_{10} is $-C(O)-NH-Z-het$ wherein *het* is selected from the group consisting of a) pyridinyl substituted with 0 or 1 methyl, b) pyrimidinyl, c) pyrazinyl, d) morpholinyl and e) oxadiazolyl; and *Z* is $-(C_0-C_1)$ alkyl;

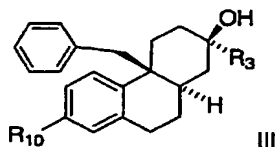
which comprises reacting a compound of formula III-B



wherein R_3 is as defined above, with a coupling reagent and a compound of formula $NH_2-Z-het$ or a salt thereof wherein *-Z* and *-het* are as defined above in an aprotic solvent at 0 °C to 100° C. More particularly, it provides this process wherein the coupling reagent is selected from the group consisting of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), dicyclohexyl carbodiimide (DCC) and hydroxybenzotriazole hydrate (HOBt).

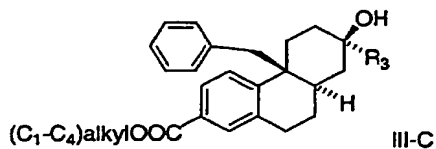
In addition, the present invention provides a process for preparing a compound of formula III

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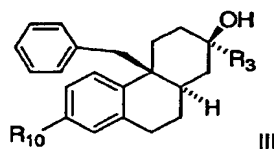
wherein R_3 is a) $-(CH_2)_2-CF_3$, b) $-(CH_2)_2-CH_3$, c) $-CH_3$, d) $-C\equiv C-CH_3$, e) $-C\equiv C-Cl$ or f) $-CF_3$; R_{10} is $-C(O)-NH-Z-het$ wherein het is selected from the group consisting of a) pyridinyl substituted with 0 or 1 methyl, b) pyrimidinyl, c) pyrazinyl, d) morpholinyl and e) oxadiazolyl; and Z is $-(C_0-C_1)$ alkyl;

which comprises reacting a compound of formula III-C



wherein R_3 is as defined above, with a tri(C_1-C_4)alkyl-aluminum compound and a compound of formula $NH_2-Z-het$ wherein $-Z$ and $-het$ are as defined above in a solvent at $0^\circ C$ to $40^\circ C$. More particularly, it provides this process wherein the tri(C_1-C_4)alkyl-aluminum compound is $Al(CH_3)_3$ and the solvent is methylene chloride.

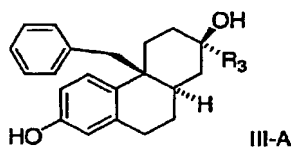
Further, the present invention provides a process for preparing a compound of formula III



wherein R_3 is a) $-(CH_2)_2-CF_3$, b) $-(CH_2)_2-CH_3$, c) $-CH_3$, d) $-C\equiv C-CH_3$, e) $-C\equiv C-Cl$ or f) $-CF_3$; R_{10} is a) $-O-C(O)-N(CH_3)_2$, b) $-O-C(O)-(1-pyrrolidinyl)$ or c) $-O-C(O)-NH-(C_0-C_3)alkyl-het$ wherein het is selected from the group consisting of 1) 2-pyridinyl, 2) 3-pyridinyl, 3) 4-pyridinyl, 4) 2-methyl-3-pyridinyl, 5) pyrazinyl, 6) morpholinyl, 7) pyrrolidinyl and 8) imidazolyl;

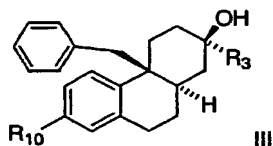
which comprises reacting a compound of formula III-A

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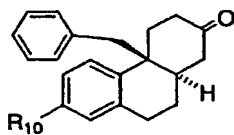
wherein R_3 is as defined above, with phosgene or triphosgene in an aprotic solvent and then with a compound selected from the group consisting of $\text{NH}(\text{CH}_3)_2$, 1-pyrrolidinyl and $\text{NH}_2-(\text{C}_0-\text{C}_3)\text{alkyl-het}$ wherein het is as defined above at 0°C to room temperature. More particularly, it provides this process wherein the solvent is toluene.

In addition, the present invention provides a process for preparing a compound of formula III



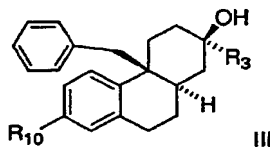
wherein R_3 is a) $-(\text{CH}_2)_2-\text{CF}_3$, b) $-(\text{CH}_2)_2-\text{CH}_3$, c) $-\text{CH}_3$, d) $-\text{C}\equiv\text{C}-\text{CH}_3$, e) $-\text{C}\equiv\text{C}-\text{Cl}$ or f) $-\text{CF}_3$; and R_{10} is $-\text{O}-(\text{C}_1-\text{C}_2)\text{alkyl-het}$ wherein het is pyridinyl substituted with 0 or 1 methyl;

which comprises reacting a compound of formula III-D



wherein R_{10} is as defined above, with R_3 -metal selected from the group consisting of $R_3\text{Li}$, $R_3\text{MgBr}$ and $R_3\text{MgCl}$ wherein R_3 is as defined above in an aprotic solvent at -78°C to room temperature.

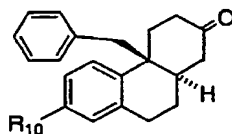
Further, the present invention provides a process for preparing a compound of formula III



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wherein R_3 is $-\text{CF}_3$; and R_{10} is $-\text{O}-(\text{C}_1-\text{C}_2)\text{alkyl-het}$ wherein het is pyridinyl substituted with 0 or 1 methyl;

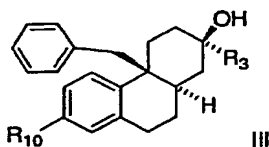
which comprises a) reacting a compound of formula III-D



III-D

wherein R_{10} is as defined above, with trimethylsilyl- CF_3 in the presence of tert-butylammonium fluoride or cesium fluoride in a protic solvent; and b) hydrolyzing the resulting intermediate with tert-butylammonium fluoride or hydrochloric acid.

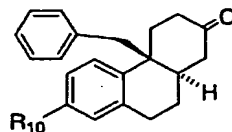
The present invention also provides process for preparing a compound of formula III



III

wherein R_3 is a) $-(\text{CH}_2)_2-\text{CF}_3$, b) $-(\text{CH}_2)_2-\text{CH}_3$, c) $-\text{CH}_3$, d) $-\text{C}\equiv\text{C}-\text{CH}_3$, e) $-\text{C}\equiv\text{C}-\text{Cl}$ or f) $-\text{CF}_3$; R_{10} is $-\text{C}(\text{O})-\text{NH}-\text{Z}-\text{het}$ wherein het is selected from the group consisting of a) pyridinyl substituted with 0 or 1 methyl, b) pyrimidinyl, c) pyrazinyl, d) morpholinyl and e) oxadiazolyl; and Z for each occurrence is independently $-(\text{C}_0-\text{C}_2)\text{alkyl}$;

which comprises reacting a compound of formula III-D

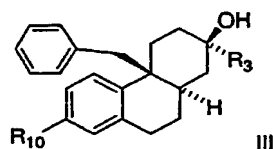


III-D

wherein R_{10} is as defined above, with $R_3\text{-metal}$ selected from the group consisting of $R_3\text{Li}$, $R_3\text{MgBr}$ and $R_3\text{MgCl}$ wherein R_3 is as defined above in an aprotic solvent at -78°C to room temperature.

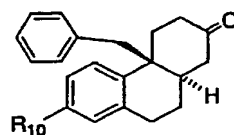
Finally, the present invention provides a process for preparing a compound of formula III

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wherein R_3 is a) $-(CH_2)_2-CF_3$, b) $-(CH_2)_2-CH_3$, c) $-CH_3$, d) $-C\equiv C-CH_3$, e) $-C\equiv C-$ Cl or f) $-CF_3$; R_{10} is $-C(O)-NH-Z-het$ wherein het is selected from the group consisting of a) pyridinyl substituted with 0 or 1 methyl, b) pyrimidinyl, c) pyrazinyl, d) morpholinyl and e) oxadiazolyl; and Z for each occurrence is independently $-(C_0-C_2)$ alkyl;

which comprises a) reacting a compound of formula III-D



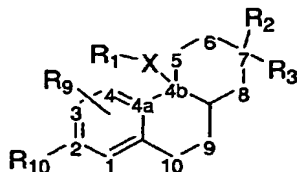
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wherein R_{10} is as defined above, with trimethylsilyl- CF_3 in the presence of tert-butylammonium fluoride or cesium fluoride in a protic solvent; and b) hydrolyzing the resulting intermediate with tert-butylammonium fluoride or hydrochloric acid.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are named according to the IUPAC or CAS nomenclature system.

In one way of naming the compounds of the present invention, the carbon atoms in the ring may be numbered as shown in the following simplified structure:



Alternatively, another way of naming the compounds of the present invention, the carbon atoms in the ring may be numbered as shown in the following simplified structure:



The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_i-C_j indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C₁-C₃ alkyl refers to alkyl of one to three carbon atoms, inclusive, or methyl, ethyl, propyl and isopropyl, and all isomeric forms and straight and branched forms thereof.

Examples of alkyl of one to nine carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, and nonyl, and all isomeric forms and straight and branched thereof.

Examples of alkenyl of two to five carbon atoms, inclusive, are ethenyl, propenyl, butenyl, pentenyl, and all isomeric forms and straight and branched forms thereof.

Examples of alkynyl of two to five carbon atoms, inclusive, are ethynyl, propynyl, butynyl, pentynyl and all isomeric forms and straight and branched forms thereof.

The terms cycloalkyl, cycloalkenyl and cycloalkynyl refer to cyclic forms of alkyl, alkenyl and alkynyl, respectively. Exemplary (C₃-C₈)cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

The term halo includes chloro, bromo, iodo and fluoro.

The term aryl refers to an optionally substituted six-membered aromatic ring, including polyaromatic rings. Examples of aryl include phenyl, naphthyl and biphenyl.

The term het refers to an optionally substituted 5-, 6- or 7-membered saturated, partially saturated or unsaturated heterocyclic ring containing from 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocyclic ring; and the nitrogen atom may be in the oxidized state giving the N-oxide form; and substituted by 0 to 3 independent substituents.

The following paragraphs describe exemplary ring(s) for the generic ring descriptions contained herein.

Exemplary five-membered rings are furyl, thienyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrrolyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrrolidinyl, 1,3-dioxolanyl, oxazolyl, thiazolyl, imidazolyl, 2H-imidazolyl, 2-imidazolyl, imidazolidinyl, pyrazolyl, 2-pyrazolyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2-dithiolyl, 1,3-dithiolyl, 3H-1,2-oxathiolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3,4-thiadiazolyl, 1,2,3,4-oxatriazolyl, 1,2,3,5-oxatriazolyl, 3H-1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, 1,3,4-dioxazolyl, 5H-1,2,5-oxathiazolyl and 1,3-oxathiolyl.

Exemplary six-membered rings are 2H-pyranyl, 4H-pyranyl, pyridinyl, piperidinyl, 1,2-dioxinyl, 1,3-dioxinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, 1,3,5-trithianyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 6H-1,3-oxazinyl, 6H-1,2-oxazinyl, 1,4-oxazinyl, 2H-1,2-oxazinyl, 4H-1,4-oxazinyl, 1,2,5-oxathiazinyl, 1,4-oxazinyl, o-isoxazinyl, p-isoxazinyl, 1,2,5-oxathiazinyl, 1,2,6-oxathiazinyl, 1,4,2-oxadiazinyl and 1,3,5,2-oxadiazinyl.

Exemplary seven-membered rings are azepinyl, oxepinyl, thiepinyl and 1,2,4-diazepinyl.

Exemplary eight membered rings are cyclooctyl, cyclooctenyl and cyclooctadienyl.

Exemplary bicyclic rings consisting of combinations of two fused partially saturated, fully saturated or fully unsaturated five or six membered rings, taken independently, optionally having one to four heteroatoms selected independently from nitrogen, sulfur and oxygen are indoliziny, indolyl, isoindolyl, 3H-indolyl, 1H-isoindolyl, indolinyl, cyclopenta(b)pyridinyl, pyrano(3,4-b)pyrrolyl, benzofuryl, isobenzofuryl, benzo(b)thienyl, benzo(c)thienyl, 1H-indazolyl, indoxazinyl, benzoxazolyl, anthranilyl, benzimidazolyl, benzthiazolyl, purinyl, 4Hquinoliziny, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxaliny, 1,8-naphthyridinyl, pteridinyl, indenyl, isoindenyl, naphthyl, tetralinyl, decaliny, 2H-1-benzopyranyl, pyrido(3,4-b)-pyridinyl, pyrido(3,2-b)-pyridinyl, pyrido(4,3-b)-pyridinyl, 2H-1,3-benzoxazinyl, 2H-1,4-benzoxazinyl, 1H-2,3-benzoxazinyl, 4H-3,1-benzoxazinyl, 2H-1,2-benzoxazinyl and 4H-1,4-benzoxazinyl.

As used herein the term "mammals" is meant to refer to all mammals, including, for example, primates such as humans and monkeys. Examples of other mammals included herein are rabbits, dogs, cats, cattle, goats, sheep and horses.

The term "treating", "treat" or "treatment" as used herein includes preventative (e.g., prophylactic) and palliative treatment.

By "pharmaceutically acceptable" it is meant the carrier, vehicle, diluent, excipient and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to the recipient thereof.

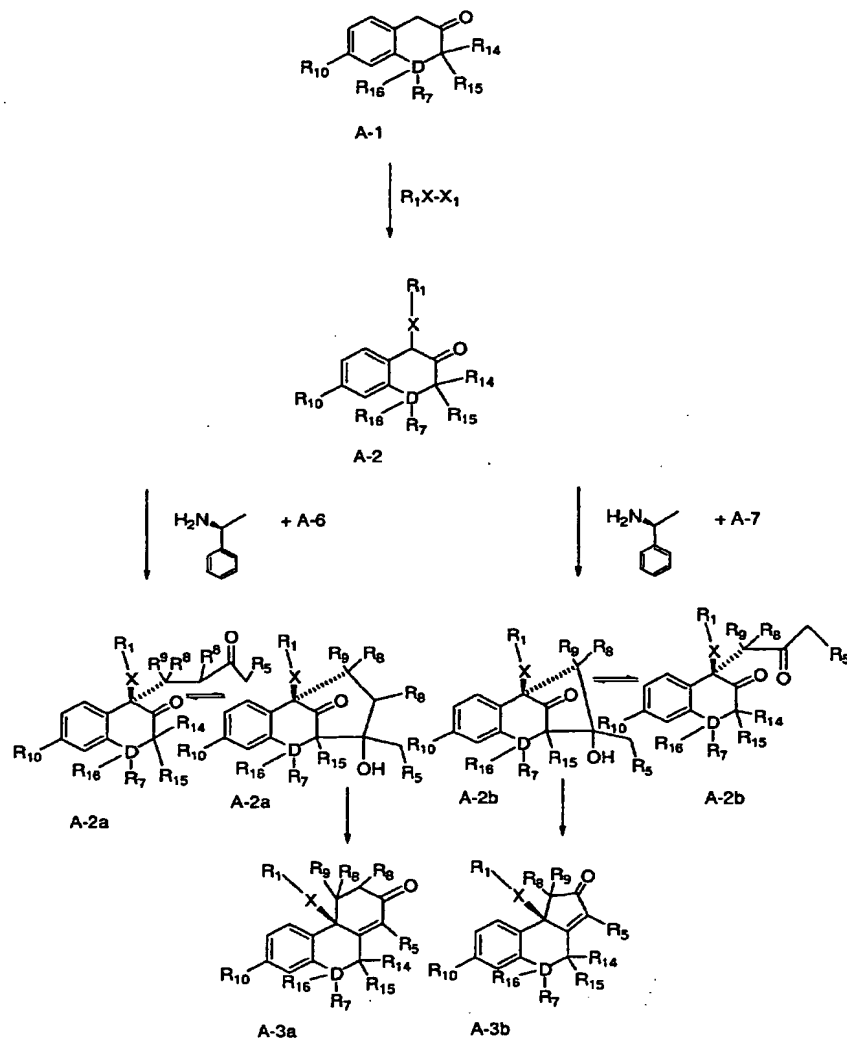
The expression "prodrug" refers to compounds that are drug precursors which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form). Exemplary prodrugs upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the Formula I compounds include but are not limited to those having a carboxyl moiety wherein the free hydrogen is replaced by (C₁-C₄)alkyl, (C₂-C₇)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-

5 (alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-
10 (alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-
(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-
5 crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such
as β-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-
15 C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl.

The compounds of formula I of the present invention are prepared as
described in the Schemes, Preparations and Examples below, or are prepared by
10 methods analogous thereto, which are readily known and available to one of ordinary
20 skill in light of this disclosure. In each of the Schemes, the R groups (e.g., R₁, R₂,
etc. . .) correspond to those noted in the Summary above. In addition, the variable n
is defined as 0 to 6. However, it will be understood by those skilled in the art that
other functionalities disclosed herein at the indicated positions of compounds of
25 15 Formula I also comprise potential substituents for the analogous positions on the
structures within the Schemes.

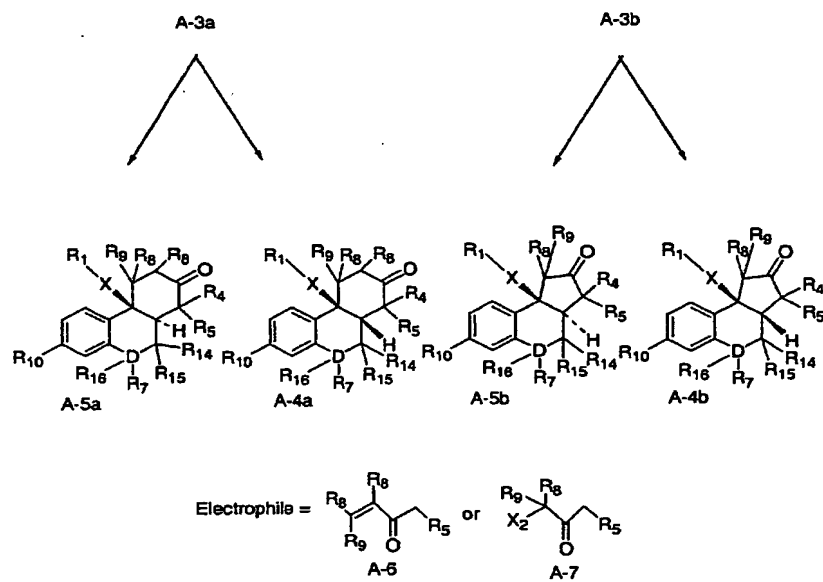
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Scheme A-1



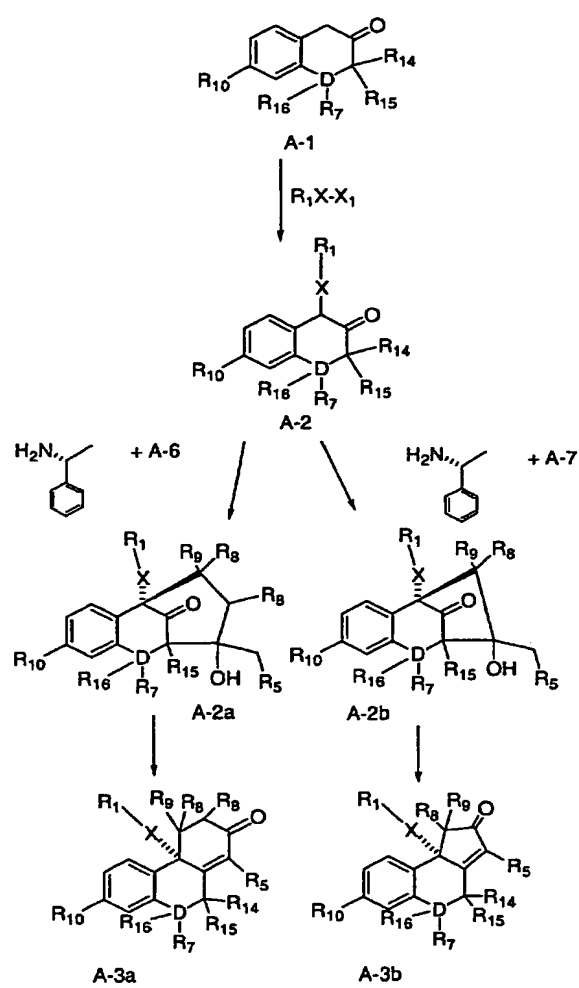
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Scheme A-1 - continued

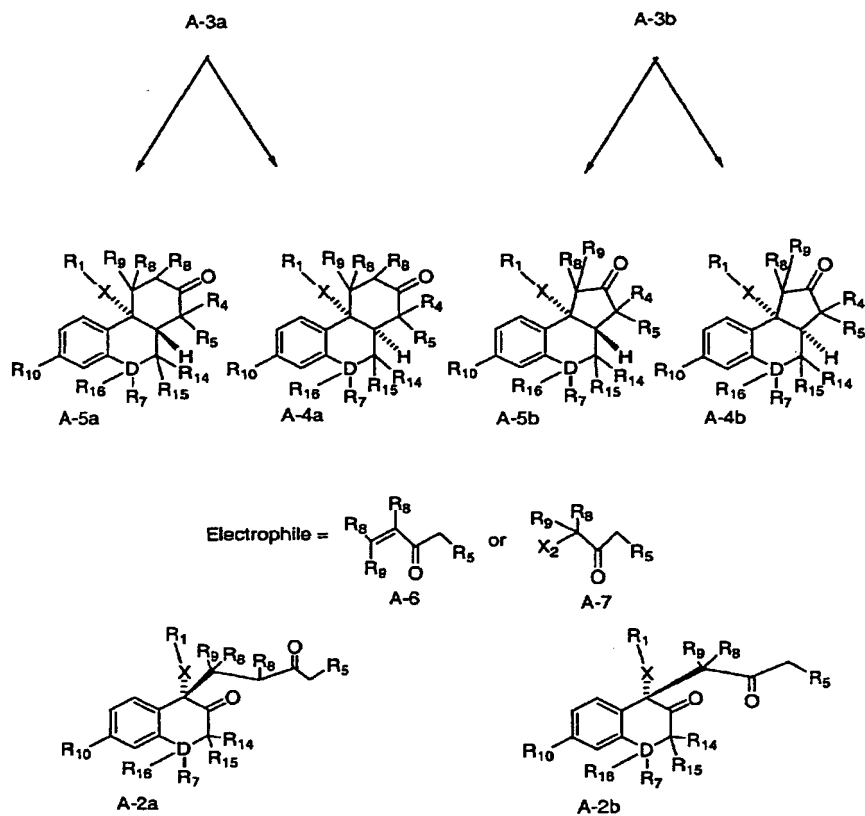


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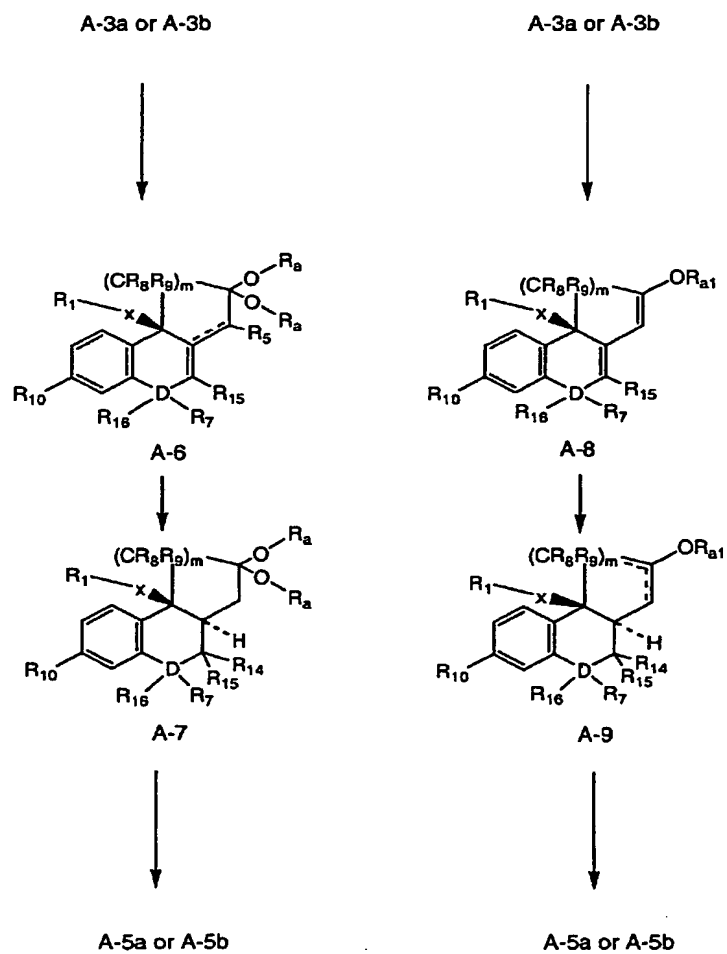
Scheme A-2



Scheme A-2 - continued



Scheme A-3



Schemes A-1, A-2 and A-3

The compound of formula A-1 (prepared as described in Org. Syn. 1971, 51, 109-112) (wherein D is methylene, substituted carbon, oxygen, sulfur or optionally protected nitrogen, R₁₀ is halogen, hydrogen, methyl ether, or benzyl ether or is as described in the Summary above, and the other variables are as defined in the Summary above) is reacted with a nitrogen-containing base, such as pyrrolidine, piperidine or morpholine, at a refluxing temperature in an aprotic solvent such as toluene, benzene, dichloromethane or dioxane, and then reacted with the alkylating agent of formula R₁X-X₁ wherein R₁X- is (C₂-C₄)alkyl straight chain or an isopropyl, t-butyl or benzyl group or is as described in the Summary above, and X₁ is a leaving group (see Francis A. Carey, in Advanced Organic Chemistry, Part A, Chapter 5.6 for examples) in dioxane, methanol, ethanol, isopropanol, DMF, DMSO or THF to give the compound of formula A-2. Typical alkylating agents are primary, secondary, benzylic or allylic halides and are preferably alkyl bromides or alkyl iodides.

Alternatively, the compound of formula A-1 is converted to its anion with a strong base, such as sodium hydride, sodium methoxide, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, potassium t-butoxide or others, in an aprotic solvent, such as dimethylformamide (DMF) or tetrahydrofuran (THF). This reaction is conducted at -78 °C to room temperature depending on the nature of the base used. The resulting anion is alkylated with the appropriate alkylating agent of formula R₁X-X₁ as defined previously to give the compound of formula A-2.

Alternatively, the compound of formula A-1 is reacted with R₁X-CHO and a base, such as pyrrolidine or an acid, such as acetic acid or hydrochloric acid, in a solvent such as toluene, benzene, methanol or ethanol. The intermediate thus obtained is then hydrogenated using a palladium on carbon catalyst or numerous other reagents such as platinum oxide or rhodium on aluminum oxide (see P.N. Rylander in Hydrogenation Methods, Academic Press, New York, 1985; Herbert O. House in Modern Synthetic Reactions, Chapter 1, pp. 1-45; and John Fried and John A. Edwards in Organic Reactions in Steroid Chemistry, Chapter 3, pp. 111-145) to give the compound of formula A-2. Alternatively, the intermediate is reacted with a reducing metal reagent, such as an alkali (group IA in the periodic table) or alkaline metal (group IIA in the periodic table), including Li, Na, or Ca, and an amine, such as

NH₃ or ethylene diamine, in an aprotic solvent, such as THF or dioxane, at -78 °C to room temperature to give the compound of formula A-2.

The compound of formula A-2 is reacted with (R)-(+)- α -methylbenzylamine (as shown in Scheme A-2) or (S)-(-)- α -methylbenzylamine (as shown in Scheme A-1) and an electrophile of formula A-6 (to form a 6-membered ring) or an electrophile of formula A-7 (to form a 5-membered ring) wherein R₅, R₆ and R₉ are as defined above in the Summary and X₂ is a leaving group that is typically a halogen such as bromide (see Francis A. Carey, in Advanced Organic Chemistry, Part A, Chapter 5.6 for examples), in an aprotic solvent such as toluene to give the C2-S or C2-R substituted intermediates of formula A-2a (which will form a six-membered ring) and of formula A-2b (which will form a five-membered ring), as shown in Schemes A-1 and A-2. These intermediates of formula A-2a and A-2b may be ring closed or ring opened as illustrated in the schemes.

Alternatively, the compound of formula A-2 is reacted with an electrophile of formula A-6 (to form a 6-membered ring) or with an electrophile of formula A-7 (to form a 5-membered ring) and a base, such as sodium methoxide or KOH, in a solvent, such as methanol, to give a racemic mixture of the intermediates of formula A-2a of Schemes A-1 and A-2 (which will form a six-membered ring) or to give a racemic mixture of the intermediates of formula A-2b of Schemes A-1 and A-2 (which will form a five-membered ring). This reaction may also give directly a racemic mixture of the products A-3a of Schemes A-1 and A-2 (which have a six-membered ring) or give directly a racemic mixture of the products A-3b of Schemes A-1 and A-2 (which have a five-membered ring), which mixtures may be resolved by chiral HPLC or by other literature methods.

The resulting intermediate of formula A-2a or A-2b is reacted with a base, such as sodium methoxide or KOH, in a solvent, such as methanol, or is reacted with an acid such as p-toluenesulfonic acid in a solvent such as toluene to give the compound of formula A-3a or A-3b, respectively, wherein the variables are as defined in the Summary above and wherein R₁₀ is halogen, hydrogen, methyl ether, or benzyl ether or is as described in the Summary above.

Alternatively, the compounds of formula A-3a or A-3b are prepared from the compound of formula A-2a or A-2b, respectively, by other reported, annulation methods, some of which are described in M.E. Jung, *Tetrahedron*, 1976, 32, pp. 3-31.

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5 The compound of formula A-3a or A-3b wherein R₁₀ is, for example, methoxy is reacted with BBr₃ or BCl₃ and tetrabutylammonium iodide or dimethylboron bromide in an aprotic solvent, such as dichloromethane or toluene at -78 °C to room temperature to give the compound of formula A-3a or A-3b wherein R₁₀ is, for example, hydroxy.

15 Alternatively, the compound of formula A-3a or A-3b wherein R₁₀ is, for example, methoxy is reacted with sodium ethanethiol in DMF or is reacted with methionine in methanesulfonic acid to give the compound of formula A-3a or A-3b wherein R₁₀ is, for example, hydroxy.

20 Also, the compound of formula A-3a or A-3b wherein R₁₀ is, for example, hydroxy may be prepared by other literature methods as described in Protecting Groups in Organic Synthesis, Second Edition, T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc. (1991) or as illustrated in Comprehensive Organic Transformation, R.C. Larock, VCH Publishers Inc. (1989), pp. 501-527.

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20 The compound of formula A-3a or A-3b wherein R₁₀ is halogen, hydrogen, methyl ether, or hydroxy or is as described in the Summary above is hydrogenated with a palladium on carbon catalyst or other reagents such as platinum oxide or rhodium on aluminum oxide (see P.N. Rylander in Hydrogenation Methods, Academic Press, New York, 1985; Herbert O. House in Modern Synthetic Reactions, Chapter 1, pp. 1-45; and John Fried and John A. Edwards in Organic Reactions in Steroid Chemistry, Chapter 3, pp. 111-145) in a variety of solvents including methanol, ethanol, and THF to yield the compound of formula A-4a or A-4b or A-5a or A-5b wherein the variables are as described in the Summary above and wherein the cis compounds are the major products.

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30 The compound of formula A-3a or A-3b wherein R₁₀ is hydrogen, methyl ether, hydroxy or is as described in the Summary above is reacted with a reducing metal reagent, such as an alkali (group IA in the periodic table) or alkaline metal (group IIA in the periodic table), including Li, Na, or Ca, and an amine, such as NH₃ or ethylene diamine, in an aprotic solvent, such as THF or dioxane, at -78 °C to room temperature to give the compound of formula A-5a or A-5b or A-4a or A-4b wherein the variables are as described in the Summary above and wherein the trans compounds are the major products.

50 Alternatively, as shown in Scheme A-3, for example, the compound of formula A-3a or A-3b of Scheme A-1 wherein R₁₀ is halogen, hydrogen, methyl ether,

hydroxy, carboxyl or is as described in the Summary above is treated with an alcohol or diol, such as methanol or ethylene glycol, and a strong acid, such as p-toluenesulfonic acid, in an aprotic solvent, such as toluene or benzene, to form a ketal intermediate of formula A-6 wherein m is one or two, R₈ is lower alkyl or wherein the R₈'s taken together with the two oxygen atoms form, for example, 1,3-dioxolane and wherein the other variables are as defined in the Summary above. Alternatively, this ketal intermediate may be prepared by other literature methods such as those described in Protecting Groups in Organic Synthesis, Second Edition, T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc. (1991). The ketal intermediate is hydrogenated using Pd(OH)₂ on carbon or other reagents, such as platinum oxide or rhodium on aluminum oxide (see P.N. Rylander in Hydrogenation Methods, Academic Press, New York, 1985; Herbert O. House in Modern Synthetic Reactions, Chapter 1, pp. 1-45; and John Fried and John A. Edwards in Organic Reactions in Steroid Chemistry, Chapter 3, pp. 111-145) in a solvent such as toluene from 15-2000 psi (which is about 1 to about 133 atm) H₂ at room temperature to 100°C. The resultant intermediate of formula A-7 is then reacted with an acid, such as p-toluenesulfonic acid, in acetone or is reacted using various literature methods, such as those described in Protecting Groups in Organic Synthesis, Second Edition, T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc. (1991), to yield the compound of formula A-5a of Scheme A-1 or the compound of formula A-5b of Scheme A-1 wherein R₁₀ is halogen, hydrogen, methyl ether, hydroxy or is as described in the Summary above, and the other variables are as defined in the Summary above. The corresponding stereoisomers of these compounds are prepared by procedures analogous to those described above.

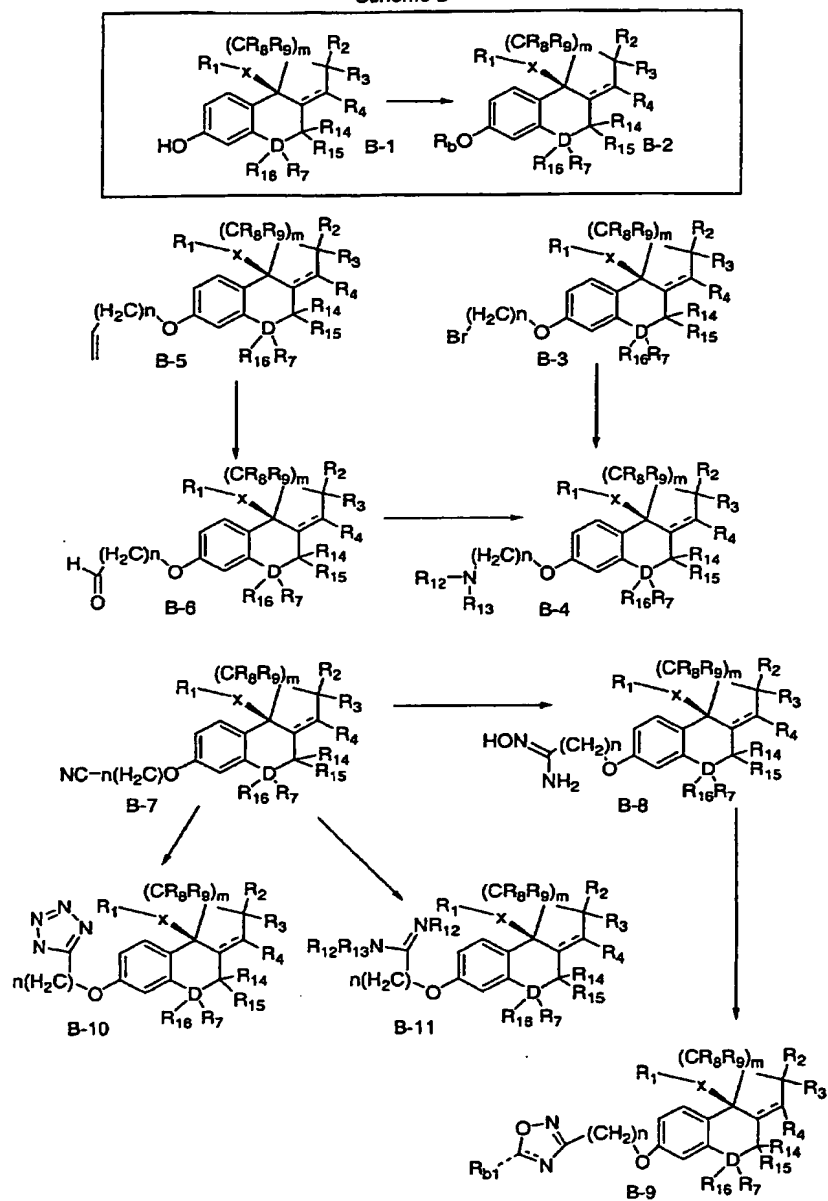
Alternatively, as shown in Scheme A-3, for example, the compound of formula A-3a or A-3b of Scheme A-1, wherein R₁₀ is halogen, hydrogen, methyl ether, hydroxy or is as described in the Summary above, is reacted with triethylorthoformate and p-toluenesulfonic acid in ethanol or toluene to form an enol ether intermediate of formula A-8 wherein m is one or two, R₁₁ is ethyl or other acyclic or cyclic lower alkyl or acyl, depending on the reagent used, and the other variables are as defined in the Summary above. Alternatively, this enol ether intermediate may be prepared by other literature methods such as those described in Protecting Groups in Organic Synthesis, Second Edition, T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc. (1991). The enol ether intermediate is then hydrogenated using Pd on CaCO₃ or

5 other reagents, such as platinum oxide or rhodium on aluminum oxide (see P.N. Rylander in Hydrogenation Methods, Academic Press, New York, 1985, Herbert O.
10 House in Modern Synthetic Reactions, Chapter 1 pp. 1-45, and John Fried and John A. Edwards in "Organic Reactions in Steroid Chemistry," Chapter 3 pp. 111-145) in a
5 variety of solvents including ethanol, methanol, and THF at 15-60 psi H₂ pressure. The resulting intermediate of formula A-9 is then reacted with an acid such as
15 aqueous HCl, in a protic solvent, such as ethanol, or is reacted under other literature conditions, such as those described in Protecting Groups in Organic Synthesis,
20 Second Edition, T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc. (1991), to yield the compound of formula A-5a of Scheme A-1 (which has a six-membered
25 ring) or the compound of formula A-5b of Scheme A-1 (which has a five-membered ring) wherein R₁₀ is halogen, hydrogen, methyl ether, hydroxy or is as described in
the Summary above, and the other variables are as defined in the Summary above. The corresponding stereoisomers of these compounds are prepared by procedures
15 analogous to those described above.

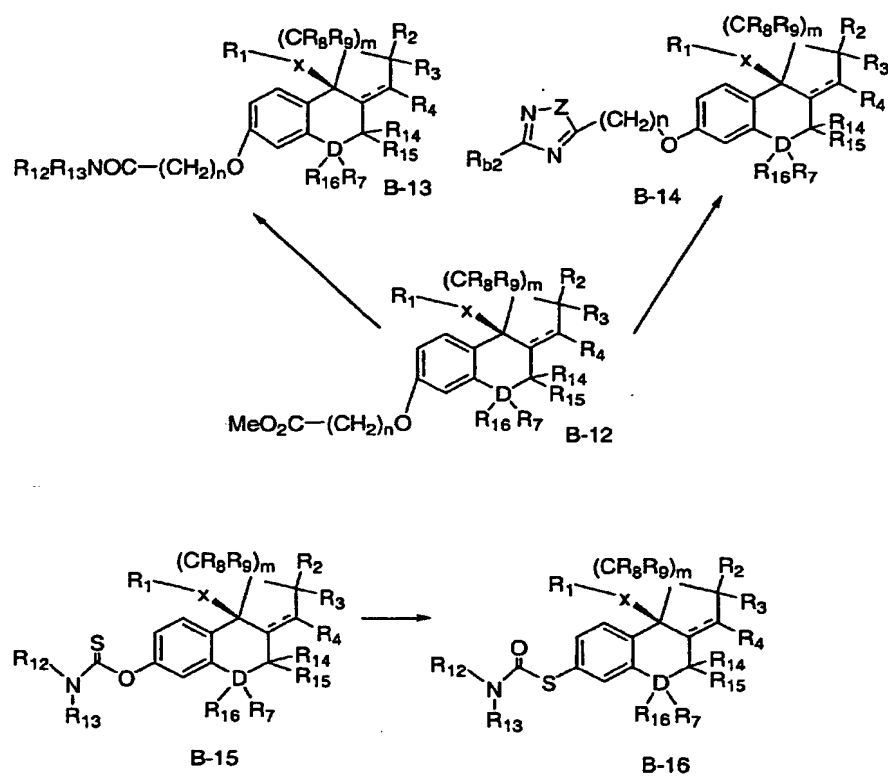
Alternatively, the resulting intermediate of formula A-3a or A-3b of Scheme A-1 is hydrogenated using Pd/BaSO₄ in a solvent such as ethanol at 15 to 200 psi H₂
30 pressure to yield the compound of formula A-5a of Scheme A-1 (which has a six-membered ring) or the compound of formula A-5b of Scheme A-1 (which has a five-
20 membered ring) wherein R₅ is COOR_{a2} and wherein R_{a2} is, for example, C₁-C₆ alkyl. Other reagents which may be used in the above hydrogenation reactions are
described in P.N. Rylander in Hydrogenation Methods, Academic Press, New York, 35 1985.

Alternatively, in Schemes A-1 and A-2, the compounds of formula A-5a or A-5b are prepared from the compounds of formula A-3a or A-3b, respectively, by other
25 reported reduction methods, some of which are described in P. Jankowski, S. Marczak, J. Wicha, *Tetrahedron*, 1998, 12071-12150.

Scheme B



Scheme B - continued



SCHEME B

The compound of formula B-1, which is obtained as described in Scheme A-1 and Scheme H, is reacted with a base, such as NaH, *t*-butoxide or Et₃N, in an aprotic solvent, such as DMF or CH₃CN, at a temperature which is between room temperature and 200°C depending on the nature of the solvent used, and is then reacted with an alkylating agent of formula R_b-X₁ wherein X₁ is a leaving group, to give the compound of formula B-2 wherein R_b is, for example, alkyl or alkyl-heterocycle and is further illustrated by a variety of different groups within the definition of R₁₀ in the Summary above. To obtain compounds of formula B-2 which are carbamates wherein R_b is, for example, -C(O)NR₁₂R₁₃ and wherein R₁₂ and R₁₃ are as defined in the Summary above, the compound of formula B-1 is reacted with a compound of formula R₁₂R₁₃-NC(O)Cl. Alternatively, to obtain compounds of formula B-2, which are carbamates wherein R_b is, for example, C(O)NR₁₂R₁₃, the compound of formula B-1 is reacted with phosgene or triphosgene in an aprotic solvent such as toluene and then with an amine of the formula R₁₂R₁₃NH. To obtain compounds of formula B-2 which are thiocarbamates wherein R_b is, for example, -C(S)NR₁₂R₁₃ and R₁₂ and R₁₃ are defined in the Summary above, the compound of formula B-1 is reacted with a compound of the formula R₁₂R₁₃NC(S)Cl. Throughout this scheme, the other variables are as defined in the Summary above.

The compound of formula B-3 wherein n is, for example, one to six (prepared by the procedures for the formula B-2 compound) is reacted with a base such as Na₂CO₃ with or without sodium iodide in an aprotic solvent, such as DMF, at a temperature which is between room temperature and 200°C, depending on the nature of the solvent used, and is then reacted with an amine of formula R₁₂R₁₃NH to obtain the compound of formula B-4 wherein n is, for example one to six and R₁₂ and R₁₃ are as defined in the Summary above.

The compound of formula B-5 wherein n is, for example, one to six, (prepared by the procedures for the formula B-2 compound) is reacted with OsO₄, N-methylmorpholine-N-oxide or K₂MnO₄ to give the corresponding diol. The diol is oxidatively cleaved with NaIO₄ or Pb(OAc)₄ to give the compound of formula B-6 wherein n is one to six, for example. Alternatively, the compound of formula B-5 is reacted with ozone and quenched with dimethyl sulfite, triphenylphosphine or other known reagent to give the compound of formula B-6. Alternatively, the compound of formula B-6 is obtained from the compound of formula B-5 by the methods illustrated

in Comprehensive Organic Transformation, R.C. Larock, VCH Publisher, Inc. (1989) pp. 595-596, pp. 615-616.

Alternatively, the compound of formula B-4 wherein n is, for example, one to six, and R₁₂ and R₁₃ are as defined in the Summary above, is obtained from the compound of formula B-6 wherein n is one to six, for example, by reductive amination. The reductive amination is typically carried out with a reducing agent, such as sodium cyanoborohydride or sodium triacetoxyborohydride, preferably at a pH of between 6 and 8. The reaction is normally performed in a protic solvent, such as methanol or ethanol, or in a mixture of solvents, such as dichloroethane/methanol, at temperature of about -78°C to about 40°C. (See A. Abdel-Magid, C. Maryanoff, K. Carson, Tetrahedron Lett. Vol. 34, Issue 31, 5595-98, 1990). Other conditions involve the use of titanium isopropoxide and sodium cyanoborohydride (R.J. Mattson et al., J. Org. Chem. 1990, 55, 2552-4) or involve the formation of the imine under dehydrating conditions followed by reduction (Comprehensive Organic Transformation, R.C. Larock, VCH Publisher, Inc (1989) pp. 421-425).

The compound of formula B-7 wherein n is, for example, one to six (prepared by the procedures for the formula B-2 compound) is reacted with a hydroxylamine or its HCl salt in a protic solvent, such as ethanol or methanol, and a base such as K₂CO₃ at a temperature between room temperature and 150 °C, depending on the nature of the solvent used, to give the compound of formula B-8 wherein n is one to six, for example.

To obtain compounds of formula B-9 wherein, for example, R_{b1} is alkyl, and n is one to six, the compound of formula B-8 wherein n is one to six, for example, is reacted with a base, such as NaH and R_{b1}-CH₂CO₂Et in an aprotic solvent such as THF at a temperature between room temperature to 140°C, depending on the nature of the solvent used. To obtain compounds of formula B-9 wherein R_{b1} is =O and n is, for example one to six, the compound of formula B-8 wherein n is one to six, for example, is reacted with a base, such as pyridine and 2-ethylhexylchloro-formate in an aprotic solvent, such as DMF. The intermediate thus obtained is refluxed in xylene or other high boiling point aromatic solvent to give the compound of formula B-9 wherein R_{b1} is =O. To obtain compounds of formula B-9 wherein R_{b1} is =S and n is, for example, one to six, the compound of formula B-8 wherein n is one to six, for example, is reacted with a base such as DBU in an aprotic solvent, such as CH₃CN and TCDI (1,1-thiocarbonyldiimidazole).

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The compound of formula B-7 wherein n is, for example, one to six, is reacted with TMSN_3 and AlMe_3 in an aprotic solvent such as toluene at between 40°C to 200°C , depending on the nature of the solvent used, to give the compound of formula B-10 wherein n is one to six, for example. Alternatively, the compound of formula B-10 is obtained by reacting the above compound of formula B-7 with NaN_3 and triethylamine or ammonium chloride in an aprotic solvent, such as DMF, at elevated temperatures.

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The compound of formula B-7 wherein n is, for example, one to six, is reacted with an amine and $\text{Al}(\text{Me})_3$ in an aprotic solvent, such as toluene, at a temperature between room temperature and 180°C , depending on the nature of the solvent used, to give the compound of formula B-11 wherein n is, for example, one to six and R_{12} and R_{13} are as defined in the Summary above. Alternatively, this compound of formula B-11 is obtained by reacting the above compound of formula B-7 with an amine in the presence of a Lewis acid, such as AlCl_3 or ZnCl_2 at 150°C to 200°C , or in the presence of an organometallic reagent, such as CuCl , CuBr or lanthanide (III) triflate. (See Tetrahedron Lett. 1993, Vol. 34, Issue 40, 6395-6398.)

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The compound of formula B-12 wherein n is, for example, one to six (prepared by the procedures for the formula B-2 compound) is reacted with an amine or its salt and $\text{Al}(\text{Me})_3$ in an aprotic solvent, such as dichloromethane, to give the compound of formula B-13 wherein n is, for example, one to six and R_{12} and R_{13} are independently hydrogen, alkyl, hydroxy or methoxy, for example or as defined in the Summary above. Alternatively, the compound of formula B-12 is hydrolyzed by the methods mentioned in Greene and Wuts, Protecting Groups in Organic Synthesis, Wiley, New York (1981) to give the corresponding free acid. The free acid thus obtained is reacted with an amine and a coupling reagent, such as DCC or EDCl , to give the above compound of formula B-13 (as illustrated in Comprehensive Organic Transformation, R.C. Larock, VCH Publisher, Inc. (1989) pp. 972-976).

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To obtain compounds of formula B-14 wherein, for example, n is one to six, Z is O and R_{b2} is alkyl or halo, the compound of formula B-12 wherein n is one to six, for example, is reacted with a base, such as NaH , in an aprotic solvent, such as THF, and $\text{NH}_2\text{C}(=\text{N}-\text{OH})\text{R}_{b2}$ wherein R_1 is alkyl at refluxing temperatures. To obtain compounds of formula B-14 wherein, for example, n is one to six, Z is N and R_{b2} is alkyl or halo, the compound of formula B-12 wherein n is one to six, for example, is

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reacted with a base, such as NaOMe, in a protic solvent, such as MeOH, and aminoguanidine nitrate.

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The compound of formula B-15 wherein R_{12} and R_{13} are as defined in the Summary above (prepared by the procedures for the formula B-2 compound) is dissolved in an aprotic solvent such as toluene and refluxed to give the compound of formula B-16 wherein R_{12} and R_{13} are as defined in the Summary above.

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Scheme C

The compound of formula C-1 (which is the same as the compound of formula B-1, see Scheme B) is treated with an acid scavenger, such as 2,6-lutidine, diisopropylethylamine, or potassium carbonate, with a trifluoromethylsulfonylation reagent, such as trifluoromethylsulfonic anhydride, N-phenyltrifluoromethanesulfonamide, or 4-nitrophenyltrifluoromethanesulfonate, with or without a catalyst, such as 4-dimethylaminopyridine (DMAP), in a solvent, such as dichloromethane, DMF or methyl-2-pyrrolidinone (NMP), from -78 °C to room temperature to obtain the compound of formula C-2 wherein R_{10} is $-\text{OS}(\text{O})_2\text{CF}_3$. Throughout this scheme, the other variables are as defined in the Summary above. Alternatively, the above compounds of formula C-2 are prepared from the compound of formula C-1 by other reported fluoroalkylsulfonylation methods, some of which are described in K. Ritter, *Synthesis*, 1993, pp. 735-762.

The compound of formula C-2 wherein the group at the R_{10} position is $-\text{OS}(\text{O})_2\text{CF}_3$ or a halogen is reacted with metalcyanide, preferably zinc(II)cyanide ($\text{Zn}(\text{CN})_2$), and with a palladium source, such as tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$), palladium(II)acetate, or tris(dibenzylidenacetone)dipalladium(0), in a solvent such as N-methyl-2-pyrrolidinone (NMP), DMF or acetonitrile, at room temperature to 120 °C to give the cyano-substituted compound of formula C-3.

To obtain the compound of formula C-4 wherein, for example, Het is tetrazolyl, the compound of formula C-3 is reacted with dibutyltin oxide (Bu_2SnO) and trimethylsilylazide (TMSN_3) in toluene from room temperature to reflux. Alternatively, the compounds of formula C-4 wherein, for example, Het is tetrazolyl are prepared from the compound of formula C-3 by other reported methods, some of which are described in S J. Wittenberger, *Organic Preparations and Procedures Int.* 1994, 26(5), pp. 499-531. Alternatively, the compound of formula C-4 wherein Het is, for example, 2-pyridyl or 3-pyridyl, is obtained by reacting the compound of formula C-2 with a heterocycle-metal, such as bromo-2-pyridyl zinc or diethyl-(3-pyridyl)borane, and a catalyst, such as $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, tetrakis(triphenylphosphine)palladium(0) ($\text{Pd}(\text{PPh}_3)_4$), or palladium acetate, and 1,1'-bis(diphenylphosphino)ferrocene, in an organic solvent, such as THF, DMF, or NMP at room temperature to 150 °C, depending on the nature of the solvent used.

5 The compound of formula C-2 is reacted under CO 1-3 atm, with a catalyst
such as palladium acetate ($\text{Pd}(\text{OAc})_2$) and 1,1'-bis(diphenylphosphino)ferrocene
10 (DPPF) or bis(diphenylphosphino)propane (DPPP), tetrakis(triphenylphosphine)
palladium(O) ($\text{Pd}(\text{PPh}_3)_4$), or tris(dibenzylidenacetone) dipalladium(O), and a base,
5 such as triethylamine or potassium carbonate, with an alcohol, such as methanol,
ethanol, or benzyl alcohol, in a solvent, such as DMF, NMP, or DMSO, at room
15 temperature to 150 °C, depending on the nature of the solvent used, to give the ester
of formula C-5, wherein R_c is, for example, alkyl or aryl.

20 An aqueous base, such as KOH, in a solvent, such as THF, is added to a
solution of the compound of formula C-5 in a solvent, such as THF. The resulting
25 solution is stirred at room temperature to reflux to give the acid of formula C-6.

A solution of the compound of formula C-6, diphenylphosphoryl azide (DPPA),
triethylamine, and an alcohol of the formula $R_c\text{OH}$, such as t-butanol, is stirred at
room temperature to reflux to give the carbamate of formula C-7, wherein, for
25 example, R_c is t-butyl.

30 The compound of formula C-6 is treated with a coupling reagent, such as 1,3-
dimethylaminopropyl-3-ethylcarbodiimide (EDC) or dicyclohexyl carbodiimide (DCC)
and hydroxybenzotriazole hydrate (HOBt), with or without a catalyst, such as 4-
dimethylaminopyridine (DMAP), and an amine, $R_{12}R_{13}\text{NH}$, in an aprotic solvent, such
20 as dichloromethane or DMF, at 0 °C to room temperature to give the amide of
formula C-8 wherein R_{12} and R_{13} are defined in the Summary above. Also, the
compounds of formula C-8 can be prepared from the compound of formula C-6 by
35 other reported, coupling methods, such as those described in Comprehensive
Organic Transformation, R.C. Larock, VCH Publishers Inc. (1989), p 972-988.

40 Alternatively, the ester of formula C-5 is added to a mixture of
trimethylaluminum ($\text{Al}(\text{CH}_3)_3$) and $R_{12}R_{13}\text{NH}$, such as 1-(3-aminopropyl)imidazole, in a
solvent, such as dichloromethane, dichloroethane (DCE), or toluene at 0 °C to room
temperature. The resulting mixture is stirred at room temperature to reflux to obtain
the amide of formula C-8 wherein, for example, R_{12} is hydrogen and R_{13} is propyl-
45 imidazol-1-yl, and are further defined in the Summary above.

50 The ester of formula C-5 is reacted with a reducing agent, such as sodium
borohydride or diisobutylaluminum hydride, in an organic solvent, such as methanol,
THF or hexane depending on the nature of the reducing agent used, at -78 °C to
room temperature, to obtain the alcohol of formula C-9 wherein R_{c1} is H. To obtain

other compounds of formula C-9, wherein, for example, R_{c1} is methyl, the compound of formula C-5 is reacted with R_{c1} -metal, such as methylmagnesium bromide, in an organic solvent, such as THF or toluene, at -78 °C to room temperature.

The carbamate of formula C-7, wherein R_c is, for example, *t*-butyl, is reacted with an acid, such as trifluoroacetic acid (TFA), in a solvent, such as dichloromethane, at -78 °C to room temperature to give the amine of formula C-10.

Also, the compound of formula C-10 may be prepared from the compound of formula C-7, wherein R_c is *t*-butyl, benzyl, or other protecting groups, by other literature methods, some of which are described in Protecting Groups in Organic Synthesis,

Second Edition, T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc. (1991).

To obtain the compound of formula C-11 wherein R_{c2} is -OSO₂-methyl, the compound of formula C-9 wherein R_{c1} is hydrogen or alkyl is reacted with a methylsulfonating reagent, such as methanesulfonyl chloride (MsCl), and an acid scavenger, such as diisopropylethylamine, in an organic solvent, such as THF or toluene at -78 °C to room temperature. To obtain the compound of formula C-11 wherein R_{c2} is Cl, the compound of formula C-9 wherein R_{c1} is hydrogen or alkyl is reacted with a chlorinating reagent, such as thionyl chloride, an acid scavenger, such as pyridine, in an organic solvent, such as methylene chloride, at -78 °C to room temperature.

The amine of formula C-10 is reacted with an acylating reagent, such as CH₃COCl and an acid scavenger, such as triethylamine or pyridine, in a solvent, such as methylene chloride or THF, at -78 °C to room temperature to give the amide of formula C-12 wherein R_{12} is as defined in the Summary above.

The compound of formula C-13 (which is obtained from the compound of formula C-6 by reacting it with N,O-dimethylhydroxylamine hydrochloride, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt and DMAP) is reacted with R_{c3} -Metal, such as ethylmagnesium bromide, in a solvent, such as THF or toluene, at -78 °C to room temperature to give the compound of formula C-14, wherein R_{c3} is, for example, ethyl.

The compound of formula C-11 and an amination reagent, such as sodium azide, in a solvent, such as DMF, NMP, or DMSO, are stirred at room temperature to 150 °C, depending on the nature of the solvent used, to give the compound of formula C-15 wherein R_{c1} is hydrogen or alkyl and R_{c4} is N₃. The resulting azide is

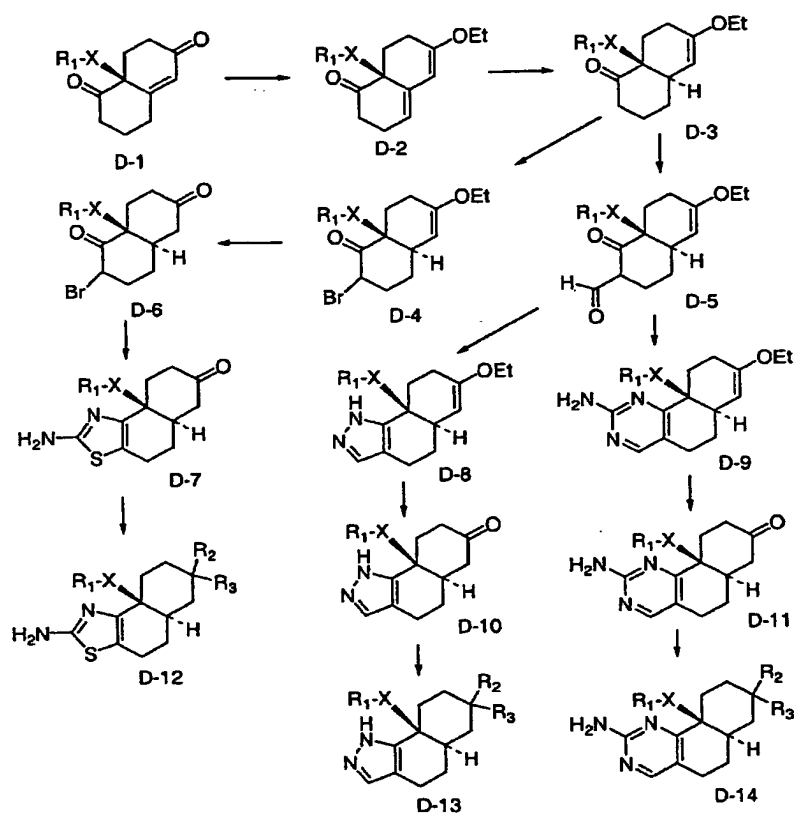
5 treated with a reducing reagent, such as triphenylphosphine (PPh_3), in a solvent or
mixture of solvents, such as THF, methanol and water, at -20°C to reflux, to give the
10 compound of formula C-15 wherein $\text{R}_{\text{C}4}$ is NH_2 .

The aldehyde of formula C-14 wherein $\text{R}_{\text{C}3}$ is hydrogen or the ketone of
5 formula C-14 wherein $\text{R}_{\text{C}3}$ is alkyl is treated with a reducing agent such as sodium
borohydride or diisobutylaluminum hydride, in an organic solvent, such as methanol,
15 THF, or hexane depending on the nature of the reducing agent used, at -78°C to
room temperature, to obtain the alcohol of formula C-16 wherein $\text{R}_{\text{C}3}$ is, for example,
ethyl.

10 The amine of formula C-15 wherein $\text{R}_{\text{C}1}$ is hydrogen or alkyl and $\text{R}_{\text{C}4}$ is $-\text{NH}_2$ is
reacted with an acylating reagent, such as CH_3COCl and an acid scavenger, such as
20 triethylamine or pyridine, in a solvent, such as methylene chloride or THF, at -78°C to
room temperature to give the amide of formula C-17 wherein R_{12} and R_{13} are as
defined in the Summary above.

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Scheme D



Scheme D

The compound of formula D-1 is prepared from commercially available cyclohexane-1,3-dione by literature procedures described in Chem. Ber., 85, 1061 (1952); Org. Syn., Coll. Vol. V, page 486; and S. Ramachandran and M.S. Newman, Org. Syn. 41, 38 (1961). It is reacted with triethylorthoformate, p-toluenesulfonic acid and ethanol in toluene to obtain the dienol ether of formula D-2. Throughout this scheme, the other variables are as defined in the Summary above.

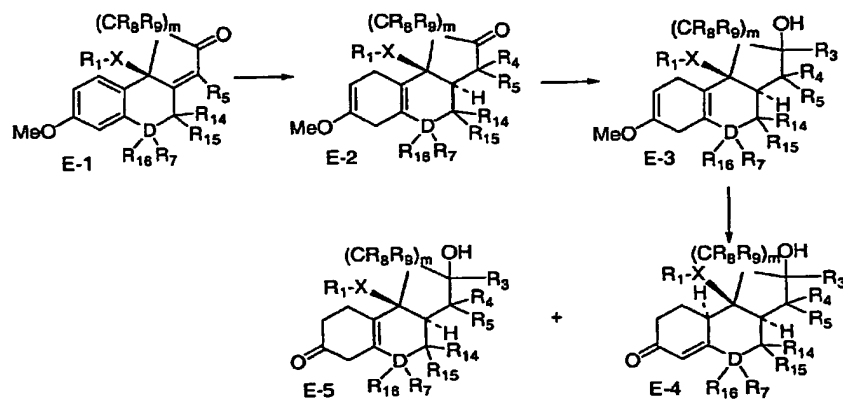
The compound of formula D-2 in ethanol or methanol is hydrogenated using 1 atm of H₂ over Pd/CaCO₃ or strontium carbonate to obtain the compound of formula D-3. The compound of formula D-3 is reacted with lithium diisopropylamide (prepared from diisopropylamine and n-butyllithium) and n-bromo-succinimide in THF to obtain the brominated compound of formula D-4. The compound of formula D-3 is reacted with ethyl formate in THF and potassium t-butoxide to obtain the carboxaldehyde of formula D-5.

The compound of formula D-4 is hydrolyzed with an aqueous acid, such as sulfuric acid, to obtain the compound of formula D-6. Likewise, once the compounds of formula D-8 and D-9 are obtained, as described below, they are hydrolyzed with aqueous acid to obtain the compounds of formula D-10 and D-11, respectively.

The compound of formula D-6 is reacted with thiourea in acetonitrile and then heated to reflux to obtain the amine-substituted thiazole compound of formula D-7. The carboxaldehyde of formula D-5 is reacted with hydrazine in ethanol/water to obtain the pyrazole compound of formula D-8. The carboxaldehyde compound of formula D-5 is reacted with a refluxing solution of sodium metal and guanidine sulfate in isopropyl alcohol to obtain the amino-substituted pyrimidine compound of formula D-9.

The compound of formula D-7 is reacted with an organometallic compound, R₃-Metal, such as R₃Li, R₃MgBr or R₃MgCl, (for example, lithio-2-chloroethyne), in an aprotic solvent such as THF at -78 °C to room temperature to obtain the compound of formula D-12 wherein R₂ and R₃ are, for example, hydroxy and chloroethynyl, respectively, and are further defined in the Summary above. Likewise, the compounds of formula D-13 and D-14 are obtained from the compounds of formula D-10 and D-11, respectively, by analogous procedures.

Scheme E



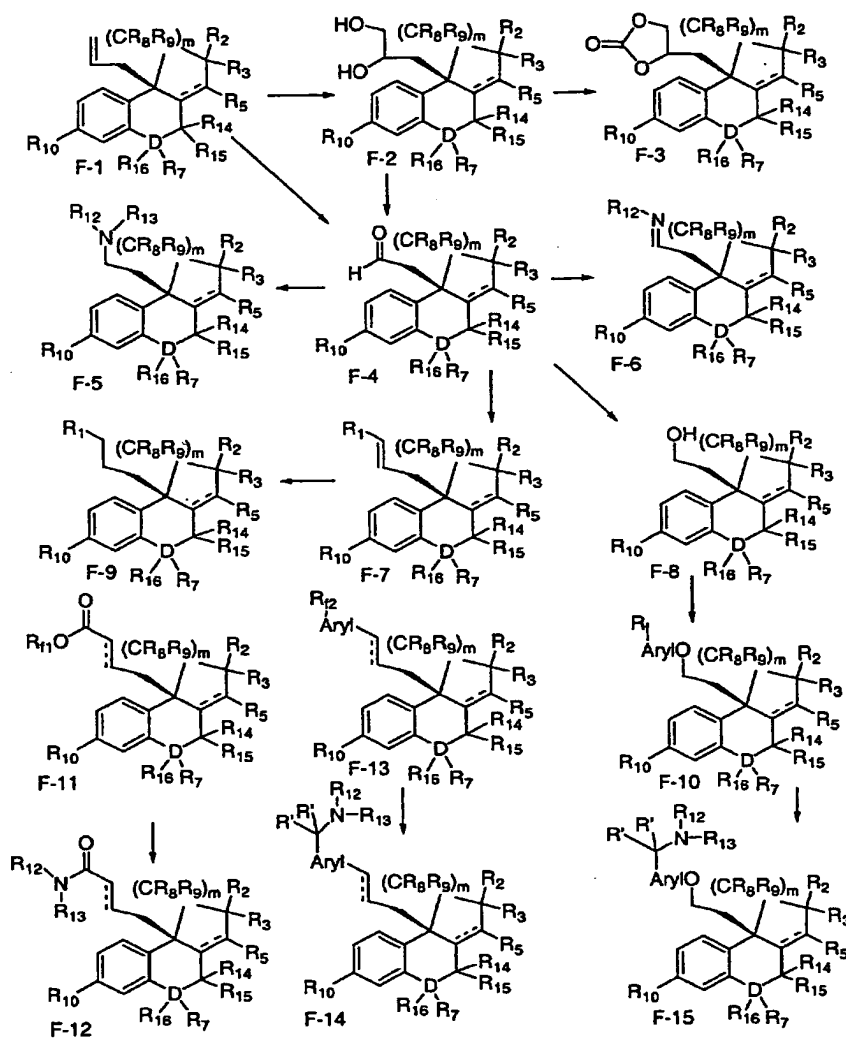
Scheme E

The compound of formula E-1 (which is the same as the compound of formula A-3a (see Scheme A) wherein R_{10} is methoxy and the other variables are as defined in the Summary above) is treated with a reducing metal reagent, such as an alkali (group IA in the periodic table) or alkaline metal (group IIA in the periodic table), including Li, Na, or Ca, an amine, such as NH_3 or ethylene diamine, and a proton source, such as *t*-butyl alcohol or ethanol, in an aprotic solvent, such as THF or dioxane, at -78 °C to room temperature to give the compound of formula E-2, wherein the variables are as described in the Summary above.

The compound of formula E-2 wherein the variables are as described in the Summary above is reacted with R_3 -Metal, such as R_3Li , R_3MgBr or R_3MgCl , wherein R_3 is, for example, alkynyl, in an aprotic solvent such as THF at low temperature to give the compound of formula of E-3 wherein the variables are as described in the Summary above.

The compound of formula E-3 is treated with an aqueous acid, such as HCl, acetic acid, or oxalic acid, in a solvent, such as THF or dioxane, at -20 °C to reflux to give the compounds of formula E-4 and E-5 wherein the variables are as defined in the Summary above in various ratios depending on the nature of the aqueous acid and the solvent used. Also, the compounds of formula E-4 and E-5 may be prepared by other literature methods as described in Protecting Groups in Organic Synthesis, Second Edition, T. W. Greene and P. G. M. Wuts, John Wiley and Sons, Inc. (1991).

Scheme F



Scheme F

The compound of formula F-1 (prepared as described in Schemes A, B, C, and H) wherein the variables are as described in the Summary above is treated with an oxidizing agent, such as osmium tetroxide in *t*-butanol, with or without an agent to regenerate the oxidizing agent, such as N-methylmorpholine-N-oxide, with or without a catalyst, such as pyridine, in a solvent, such as methylene chloride, at 0 °C to room temperature to obtain the diol compound of formula F-2 wherein the variables are as described in the Summary above.

The compound of formula F-2 wherein the variables are as described in the Summary above is reacted with a carbonylation reagent, such as carbonyldiimidazole, diphosgene or phosgene, in a solvent, such as THF or methylene chloride, at 0 °C to reflux to obtain the (2-oxo-1,3-dioxolan-4-yl)methyl compound of formula F-3 wherein all the variables are as described in the Summary above.

The diol compound of formula F-2 wherein the variables are as described in the Summary above is oxidatively cleaved with an oxidation reagent, such as sodium periodate (NaIO₄), with or without an acid scavenger, such as sodium bicarbonate, in a solvent, such as methylene chloride, at 0 °C to room temperature to obtain the aldehyde of formula F-4 wherein the variables are as described in the Summary above.

Alternatively, the compound of formula F-1 wherein the variables are as described in the Summary above is treated concomitantly with an oxidation reagent, such as osmium tetroxide in *t*-butanol, and an oxidative cleavage reagent, such as sodium periodate (NaIO₄), with or without an agent to regenerate the oxidizing agent, such as N-methylmorpholine-N-oxide, with or without a catalyst, such as pyridine, in a solvent mixture, such as dioxane and water, at 0 °C to room temperature to obtain the aldehyde of formula F-4 wherein the variables are as described in the Summary above.

Alternatively, the compound of formula F-1 wherein the variables are as described in the Summary above is treated with ozone in a solvent, such as THF, at -78°C to 0°C followed by treatment with a reducing agent, such as dimethyl sulfide, at -78°C to room temperature to obtain the aldehyde of formula F-4 wherein the variables are as described in the Summary above.

5 The aldehyde of formula F-4 wherein the variables are as described in the
Summary above is treated with an amine, ($\text{NHR}_{12}\text{R}_{13}$, for example, piperidine), with or
10 without a drying agent, such as molecular sieves or magnesium sulfate, with a
reducing agent, such as sodium triacetoxyborohydride ($\text{NaBH}(\text{OAc})_3$) or sodium
5 cyanoborohydride (NaCNBH_3), in a solvent or a mixture of solvents, such as acetic
acid and/or dichloromethane, at 0 °C to room temperature to obtain the compound of
15 formula F-5, wherein, for example, R_{12} and R_{13} taken together are piperidiny1 and
wherein the other variables are as described in the Summary above.

20 The oxime-containing compound of formula F-6 wherein R_{12} is hydroxy or
alkoxy and wherein the other variables are as described in the Summary above, is
prepared by reacting the formula F-4 compound wherein the variables are as
25 described in the Summary above with hydroxylamine or an alkoxyamine or an HCl
salt, with or without a base, such as KHCO_3 or pyridine, in a solvent, such as
methanol, ethanol or pyridine, at 0 °C to reflux.

30 An olefination reagent, such as $\text{PO}(\text{OR}_1)_2\text{CH}_2\text{R}_1$, is treated with a base, such
as lithium diisopropyl amine (LDA) or n-butyl lithium, and is reacted with the aldehyde
of formula F-4 wherein the variables are as described in the Summary above in a
solvent, such as THF at -78 °C to room temperature to obtain the alkenyl compound
of formula F-7 wherein the variables are as described in the Summary above.

35 The aldehyde of formula F-4 wherein the variables are as described in the
Summary above is treated with a reducing agent, such as diisobutylaluminum hydride
(DIBAL) in hexane or sodium borohydride (NaBH_4), in a solvent, such as THF or
methanol, at -78 °C to room temperature to obtain the alcohol of formula F-8 wherein
the variables are as described in the Summary above.

40 The alkenyl compound of formula F-7 wherein the variables are as described
in the Summary above is hydrogenated using hydrogen with a palladium on carbon
catalyst or other reagents such as platinum oxide or rhodium on aluminum oxide (see
P.N. Rylander in Hydrogenation Methods, Academic Press, New York, 1985; Herbert
O. House in Modern Synthetic Reactions, Chapter 1, pp. 1-45; and John Fried and
45 John A. Edwards in Organic Reactions in Steroid Chemistry, Chapter 3, pp. 111-145)
in a variety of solvents including methanol, ethanol and THF to obtain the compound
of formula F-9 wherein the variables are as described in the Summary above.

50 The alcohol of formula F-8 is coupled with $\text{R}_1\text{-ArylOH}$, utilizing an
azocarboxylate such as diethylazodicarboxylate (DEAD), a trialkyl phosphine such as

triphenylphosphine (PPh_3) in a solvent, such as methylene chloride, to obtain the compound of formula F-10 wherein R_1 is formyl and other aromatic substituents as described in the Summary above and the other variables are as defined in the Summary above. Alternatively, formula F-10 compounds are prepared by reacting the compound of formula F-8 with p-toluenesulfonyl chloride. The resulting intermediate in DMF is reacted with an alkali metal salt of $\text{R}_1\text{-ArylOH}$ to give the compound of formula F-10.

The ester of formula F-11 (prepared from the aldehyde of formula F-4 by an olefination procedure described above) wherein R_{11} is, for example, methyl, and the other variables are as described in the Summary above is reacted with an aqueous base, such as KOH, in a solvent, such as THF, and the resulting solution is heated and stirred at room temperature to reflux to obtain the acid of formula F-11 wherein R_{11} is hydrogen and all the additional variables are as described in the Summary above.

The compound of formula F-11 wherein R_{11} is hydrogen and the other variables are as described in the Summary above is treated with a coupling reagent, such as 1,3-dimethylaminopropyl-3-ethylcarbodiimide (EDC) or dicyclohexyl carbodiimide (DCC) and hydroxybenzotriazole hydrate (HOBt), with or without a catalyst, such as 4-dimethylaminopyridine (DMAP), and an amine ($\text{R}_{12}\text{R}_{13}\text{NH}$, such as pyrrolidine), in an aprotic solvent, such as dichloromethane or DMF, at 0 °C to room temperature to obtain the compound of formula F-12 wherein, for example R_{12} and R_{13} taken together are pyrrolidinyl, and the other variables are as described in the Summary above. Also, the compounds of formula F-12 are prepared from the compounds of formula F-11 by other reported, coupling methods, some of which are described in Comprehensive Organic Transformation, R.C. Larock, VCH Publishers Inc. (1989), pp. 972-988.

The compound of formula F-13 wherein R_2 is COOR_3 , wherein R_3 is, for example, methyl, and wherein the other variables are as defined in the Summary above (prepared from the aldehyde of formula F-4 by an olefination procedure described above) is hydrolyzed with an aqueous base, such as KOH, in a solvent, such as THF, and the resulting solution is stirred at room temperature to reflux to give the compound of formula F-13 wherein R_2 is COOH and the other variables are as described in the Summary above.

5 The compound of formula F-13 wherein R_2 is COOH is treated with a
coupling reagent, such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) or
10 dicyclohexyl carbodiimide (DCC) and hydroxybenzotriazole hydrate (HOBt), with or
without a catalyst, such as 4-dimethylaminopyridine (DMAP), and an amine
5 ($R_{12}R_{13}NH$, such as pyrrolidine), in an aprotic solvent, such as dichloromethane or
DMF, at 0 °C to room temperature to obtain the compound of formula F-14 wherein,
15 for example R_{12} and R_{13} taken together are pyrrolidinyl, R' and R' are taken together
to form =O, and the other variables are as described in the Summary above. Also,
the compounds of formula F-14 are prepared from the compounds of formula F-13 by
10 other reported, coupling methods, some of which are described in Comprehensive
Organic Transformation, R.C. Larock, VCH Publishers Inc. (1989), pp. 972-988.

20 The compound of formula F-13 wherein R_2 is CHO and the other variables
are as described in the Summary above (which is prepared analogously to the
compound of formula F-7) is treated with an amine, ($NHR_{12}R_{13}$, for example,
25 piperidine), with or without a drying agent, such as molecular sieves or magnesium
sulfate, and with a reducing agent, such as sodium triacetoxyborohydride
15 ($NaBH(OAc)_3$) or sodium cyanoborohydride ($NaCNBH_3$), in a solvent or a mixture of
solvents, such as acetic acid and/or dichloromethane, at 0 °C to room temperature to
30 obtain the compound of formula F-14, wherein, for example, R_{12} and R_{13} taken
together with the nitrogen atom are piperidinyl, each R' is H, and wherein the other
20 variables are as described in the Summary above.

35 The protected compound of formula F-13 wherein R_2 is, for example, -
 $CH_2OTBDMS$ is prepared from the aldehyde of formula F-4 by Wittig coupling as
described above. This compound is deprotected to the alcohol by using
25 tetrabutylammonium fluoride in a solvent, such as tetrahydrofuran. This alcohol
wherein R_2 is CH_2OH is reacted with methanesulfonyl chloride, diisopropylethylamine
40 and a primary or secondary amine, such as morpholine, to give the compound of
formula F-14 wherein R_{12} and R_{13} taken together are, for example, morpholinyl, each
 R' is H and the other variables are as described in the Summary above.

45 30 The compound of formula F-10 wherein R_1 is CHO and the other variables are
as described in the Summary above (which is prepared as described above) is
treated with an amine, ($NHR_{12}R_{13}$, for example, piperidine), with or without a drying
agent, such as molecular sieves or magnesium sulfate, and with a reducing agent,
50 such as sodium triacetoxyborohydride ($NaBH(OAc)_3$) or sodium cyanoborohydride

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Scheme G

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5 as defined in the Summary above (which is prepared according to the procedures in
Schemes A and H) is reacted with an aldehyde or ketone such as $R_{12}C(O)R_{13}$ and
10 with sodium triacetoxyborohydride ($Na(OAc)_3BH$) or sodium cyanoborohydride
($NaCNBH_3$) as reducing agents to give the reductive amination product of formula G-
5 2 wherein Z_1 is N and the other variables are as defined in the Summary above.
Alternatively, the compound of formula G-2 is prepared from the compound of
formula G-1 by other reductive amination methods known in the art, such as those
15 disclosed for the preparation of the compound of formula B-4 in Scheme B above.

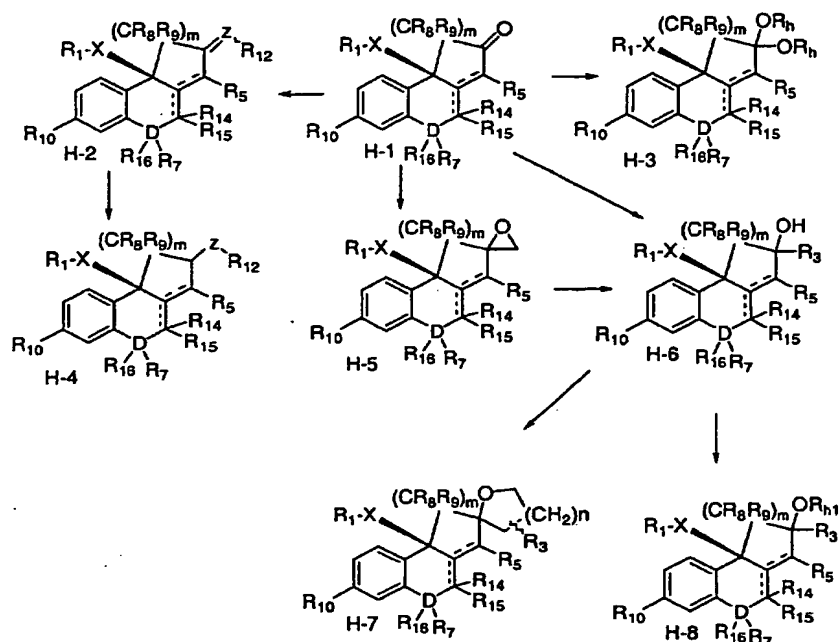
The compound of formula G-1 wherein Z_1 is NH_2 or OH is reacted with a
10 coupling reagent, such as 1,3-dimethylaminopropyl-3-ethylcarbodiimide (EDC) or
dicyclohexyl carbodiimide (DCC) and hydroxybenzotriazole hydrate (HOBt), and a
base, such as 4-dimethylaminopyridine (DMAP) or triethylamine, in an aprotic solvent,
20 such as methylene chloride, and an acid to give the compound of formula G-3
wherein Z_1 is O or NR_{12} , R_9 is for example, alkyl and the other variables are as
15 defined in the Summary above. Alternatively, the compound of formula G-3 is
obtained from the compound of formula G-1 by standard acylation, such as treating
the compound of formula G-1 with a base, such as pyridine, and an acyl halide or
25 acid anhydride in an aprotic solvent to give the compound of formula G-3.

The compound of formula G-4 wherein Z_1 is O or NR_{12} and the other variables
30 are as defined in the Summary above is obtained from the compound of formula G-1
according to the procedures described in Scheme B, such as the preparation of the
carbamate of formula B-2 wherein R_6 is $-C(O)NR_{12}R_{13}$. Alternatively, the compound
of formula G-4 wherein Z_1 is $NHBoc$ is reacted with a base, such as $n-BuLi$, in an
35 aprotic solvent and an amine to give the compound of formula G-4 wherein Z_1 is NH.

25 The compound of the formula G-1 is reacted with the compound of formula
 $R_{91}SO_2Cl$ and a base, such as triethylamine, in an aprotic solvent, such as THF, to
give the compound of formula G-5 wherein Z_1 is O or NR_{12} , R_{91} is, for example, alkyl
40 and the other variables are as defined in the Summary above.

The compound of formula G-1 wherein Z_1 is $-NH_2$ and the other variables are
30 as defined in the Summary above is reacted with $(Me_2NCH=N)_2$ in an aprotic solvent
such as toluene and with an acid, such as p-toluenesulfonic acid, to give the
45 compound of formula G-6 wherein the variables are as defined in the Summary
above.

Scheme H



Scheme H

The compound of formula H-1 wherein the variables are as described in the Summary above (which is prepared by the procedures in Scheme A above) is reacted with reagents such as $P(R_{12})_3CH_2R_{12}$ or $PO(OR_{12})_2CH_2R_{12}$ wherein R_{12} is lower alkyl or aryl and the other variables are as defined in the Summary above and a base such as lithium diisopropylamide (LDA) or sodium hydride (NaH) in an aprotic solvent, such as THF or DMF, to give the compound of formula H-2 wherein Z is CH , and R_{12} and the other variables are as defined in the Summary above.

The compound of formula H-1 is reacted with the compound of formula H_2NOR_{12} or its hydrochloride salt in ethanol or methanol, with or without sodium acetate (NaOAc), at room temperature or at the refluxing temperature of the solvent, to give the compound of formula H-2 wherein Z is N , and R_{12} and the other variables are as defined in the Summary above.

5 The compound of formula H-1 is reacted with $R_h\text{OH}$ wherein R_h is, for example, lower alkyl or ethylene glycol, and an acid such as p-toluenesulfonic acid in an aprotic solvent such as toluene at reflux temperature under Dean-Stark trap to remove water to give the compound of the formula H-3 wherein R_h is, for example, lower alkyl or wherein R_h 's taken together with the two oxygen atoms form, for example, 1,3-dioxolane, and the other variables are as defined in the Summary above.

10 The compound of the formula H-2 wherein Z is CH, R_{12} is, for example, alkyl and the other variables are as defined in the Summary above is reacted with H_2 , and Pd/C or other reagents as described by P. N. Rylander in Hydrogenation Methods, Academic Press, New York, 1985 in a solvent, such as methanol, to give the compound of formula H-4 wherein Z is CH, R_{12} is, for example, alkyl, and the other variables are as defined in the Summary above.

15 The compound of the formula H-2 wherein Z is N, R_{12} is, for example, alkyl and the other variables are as defined in the Summary above is reacted with hydrochloric acid in methanol and borane-trimethyl-amine complex (Me_3NBH_3) or other reducing reagents to give the compound of formula H-4 wherein Z is NH, R_{12} is alkyl and the other variables are as defined in the Summary above.

20 Alternatively, the compound of formula H-4 is obtained from the compound of formula H-2 by other hydrogenation procedures which are known and available in the art.

25 The compound of formula H-1 is reacted with trimethylsulfonium iodide ($(\text{CH}_3)_3\text{S}^+\text{I}^-$) or trimethylsulfoxonium iodide ($(\text{CH}_3)_3\text{S}^+\text{O}^-\text{I}^-$) and a base, such as potassium t-butoxide, in an aprotic solvent such as DMF to give the compound of formula H-5 wherein the variables are as defined in the Summary above.

30 Alternatively, the compound of formula H-5 is obtained from the compound of formula H-1 by an analogous method to that illustrated in Comprehensive Organic Transformation, R.C. Larock, VCH Publishers Inc. (1989), pp. 468-470.

35 The compound of formula H-1 is reacted with $\text{R}_3\text{-Metal}$, such as R_3Li , R_3MgBr or R_3MgCl , wherein R_3 is, for example, alkynyl or alkyl in an aprotic solvent such as THF at low temperature to give the compound of formula H-6 wherein R_3 is alkynyl or alkyl and the other variables are as defined in the Summary above.

40 The compound of formula H-1 is reacted with TMSCF_3 and TBAF as described in G.A. Olah et al., *J.Am.Chem.Soc.* (1989) 111, 393, to give the

compound of formula H-6 wherein R_3 is $-CF_3$ and the other variables are as defined in the Summary above. Alternatively, the compound of formula H-1 is treated with other $-CF_3$ nucleophiles which are known and available in the literature including, but not limited to, that disclosed by J. Russell, N. Roques, Tetrahedron, 1998, 54, 13771-13782.

Alternatively, the compound of formula H-5, wherein the variables are as defined in the Summary above, is reacted with R_3 -Metal such as R_3Li , R_3MgBr , or R_3MgCl wherein R_3 is, for example, alkyl in an aprotic solvent such as THF at low temperature to give the compound of formula H-6 wherein R_3 is, for example, $-CH_2$ -alkyl, and the other variables are as defined in the Summary above. Alternatively, the compound of formula H-5 wherein the variables are as defined in the Summary above is reacted with R_3 -X-Metal, such as R_3ONa , R_3SNa , R_3OK , R_3OLi or R_3SLi wherein R_3 is, for example, alkynyl and X is O or S in an aprotic solvent such as THF, at room temperature to the refluxing temperature of the solvent used, to give the compound of the formula H-6 wherein R_3 is, for example, $-O-CH_2$ -alkynyl or $-S-CH_2$ -alkynyl and the other variables are as defined in the Summary above. Alternatively, the compound of formula H-5 wherein the variables are as defined in the Summary above is reacted with an amine in an aprotic solvent such as THF, at room temperature to the refluxing temperature of the solvent used, to give the compound of the formula H-6 wherein R_3 is $-CH_2-NR_{12}R_{13}$ and the other variables are as defined in the Summary above.

The compound of formula H-6 wherein R_3 is alkynyl and the other variables are as defined in the Summary above is reacted with H_2 , Pd/C, or PtO_2 to give the corresponding saturated alkyl product. The compound of formula H-6 wherein R_3 is alkynyl and the other variables are as defined in the Summary above is reacted with $LiAlH_4$ in an aprotic solvent such as THF to give the corresponding trans-alkenyl product. The compound of formula H-6 wherein R_3 is alkynyl and the other variables are defined in the Summary above is reacted with H_2 and Lindlar catalyst to give the corresponding cis-alkenyl product. Alternatively, these compounds are obtained using other conditions as described in Modern Synthetic Reactions, Herbert O. House, Ed., Chapters 1 & 2.

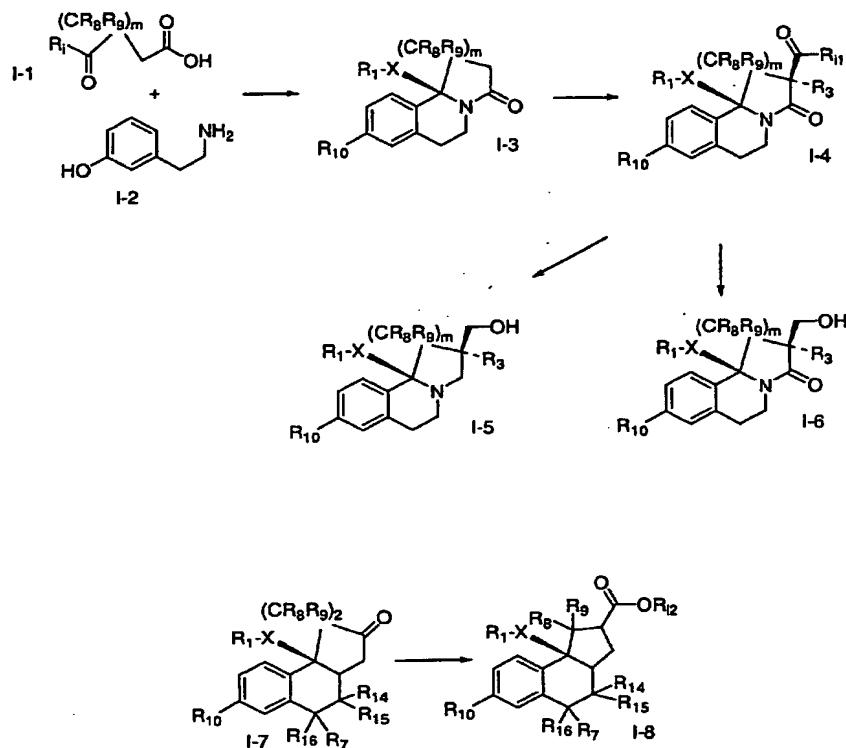
The compound of formula H-6 wherein R_3 is hydroxyalkyl and the other variables are as defined in the Summary above is reacted with an acid such as p-toluenesulfonic acid in an aprotic solvent such as toluene at reflux temperature to

5 give the compound of formula H-7 wherein n is 1 or 2 and the other variables are as
defined in the Summary above. Alternatively, the compound of formula H-6 wherein
10 R_3 contains a leaving group such as halogen, mesylate, tosylate or triflate and the
other variables are as defined in the Summary above is reacted with a base such as
5 NaH in an aprotic solvent such as THF to give the compound with the formula H-7
wherein n is 1 or 2 and the other variables are as defined in the Summary above.

15 The compound of formula H-6 wherein the variables are as defined in the
Summary above is reacted with a base such as Et_3N or NaH and $R_{n1}X$ wherein, for
example, R_{n1} is methyl and X is halogen or other leaving group in an aprotic solvent
10 such as THF or methylene chloride to give the compound of formula H-8 wherein, for
example, R_{n1} is methyl and the other variables are as defined in the Summary above.
20 Alternatively, the compound of formula H-6 wherein the variables are as defined in
the Summary above is reacted with N_2CHR_{n1} , wherein, for example, R_{n1} is methyl,
and $Rh(OAc)_3$, in an aprotic solvent such as methylene chloride to give the compound
25 of formula H-8 wherein, for example, R_m is methyl and the other variables are as
defined in the Summary above.

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Scheme I



Scheme I

The compound of formula I-1 wherein R₁ is, for example, benzyl, and wherein m is one, is prepared as described in L.M. Fuentes, G.L. Larson, *Tetrahedron Lett.* 1982, 23 (3), pp. 271-274. The compound of formula I-1 wherein R₁ is, for example, benzyl, and wherein m is two, is prepared as described in A. Ijima, K. Takashi, *Chem Pharm. Bull.* 1973, 21(1), pp. 215-219. The compound of formula I-1 and the compound of formula I-2 (which is commercially available) (or a salt of the compound of formula I-2, such as the hydrobromide or hydrochloride salt) are reacted in a

5 solvent, such as isopropanol, at between 200°C and 300 °C to obtain the compound
of formula I-3 wherein R₁₀ is hydroxy and the other variables are as described in the
10 Summary above.

The compound of formula I-3 wherein R₁₀ is hydroxy and the other variables
5 are as described in the Summary above, which is in a solvent, such as DMF, is
reacted with a base, such as potassium t-butoxide in t-butanol, and an electrophile,
15 such as benzyl bromide, at 0°C to 100°C to obtain the compound of formula I-3
wherein R₁₀ is, for example, -O-benzyl.

The compound of formula I-3 wherein R₁₀ is, for example, -O-benzyl, and the
10 other variables are as defined in the Summary above, which is in a solvent, such as
THF, is treated with 2 eq. of a strong base, such as lithium diisopropylamide in THF,
20 at -78°C to 0°C, and is then treated with an electrophile, such as methylchloroformate
(ClCOOMe), at -78° to 0° C. A second electrophile, such as propyl iodide, is added
25 and the resulting mixture heated to between 0°C to 55°C to give the compound of
15 formula I-4 wherein, for example, R₁₀ is -O-benzyl, R₃ is propyl, R₁₁ is methoxy and
the other variables are as defined in the Summary above.

The compound of formula I-4 wherein, for example, R₁₀ is -O-benzyl, R₃ is
30 propyl, R₁₁ is methoxy and the other variables are as defined in the Summary above is
hydrogenated to obtain the compound of formula I-4 wherein, for example, R₁₀ is
20 hydroxy, R₃ is propyl, R₁₁ is methoxy and the other variables are as defined in the
Summary above, using ammonium formate(NH₄⁺HCOO⁻) in methanol and a
palladium on carbon catalyst at refluxing temperatures. The compound of formula I-5,
35 which is prepared below, wherein, for example, R₁₀ is -O-benzyl or -O-methyl, R₃ is
propyl and the other variables are as defined in the Summary above, is treated with
25 boron tribromide (BBr₃) in methylene chloride at -78 °C to room temperature to obtain
the corresponding compound wherein R₁₀ is hydroxy. Likewise, the compound of
40 formula I-6, which is prepared below, wherein, for example, R₁₀ is -O-benzyl, R₃ is
propyl and the other variables are as defined above, is cleaved under similar
conditions. A variety of other hydrogenating agents and conditions are known and
45 available in the art, such as using H₂ on a palladium on carbon catalyst in methanol.

30 The compound of formula I-4 wherein, for example, R₁₀ is -O-benzyl, R₃ is
propyl, R₁₁ is methoxy and the other variables are as defined in the Summary above,
is reacted with a reducing agent, such as lithium aluminum hydride (LiAlH₄), in a

5 solvent, such as THF, at 0 °C to refluxing temperatures to obtain the compound of
10 formula I-5 wherein, for example, R₁₀ is -O-benzyl, R₃ is propyl and the other
variables are as defined in the Summary above.

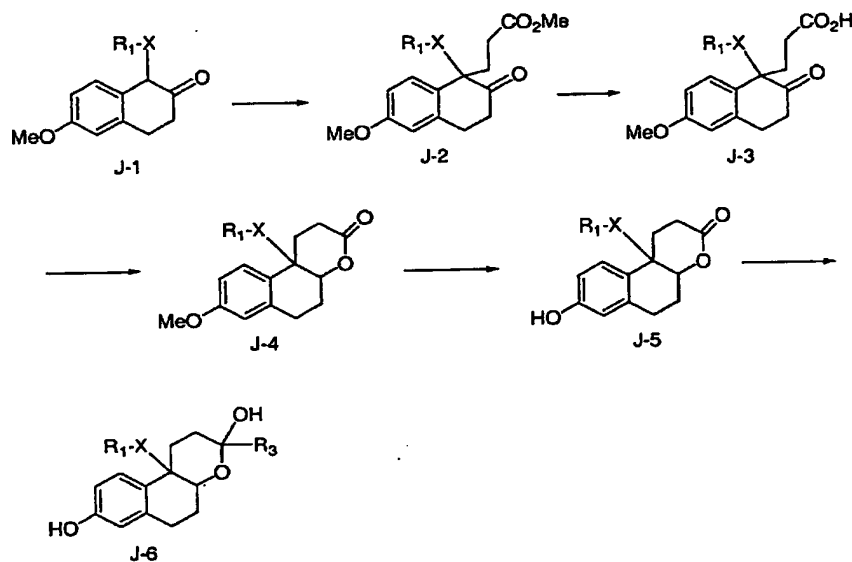
5 The compound of formula I-4 wherein, for example, R₁₀ is -O-benzyl, R₃ is
propyl, R₁₁ is methoxy and the other variables are as defined in the Summary above,
15 is reacted with a reducing agent, such as lithium borohydride (LiBH₄), in a solvent,
such as THF, at 0°C to room temperature to obtain the compound of formula I-6
wherein, for example, R₁₀ is -O-benzyl, R₃ is propyl and the other variables are as
20 defined in the Summary above. A variety of other esterifying conditions are known
and available in the art.

20 The compound of formula I-7 (which is prepared by procedures described in
Scheme A) is reacted with thallium trinitrite.3H₂O in a solvent, such as methylene
chloride to obtain the acid of formula I-8 wherein R₁₂ is H and wherein, for example,
25 R₁-X- is benzyl and R₁₀ is CH₃-C(O)-O-, and wherein these variables are further
defined in the Summary above.

15 The acid of formula I-8 wherein R₁₂ is H and wherein, for example, R₁-X- is
benzyl and R₁₀ is CH₃-C(O)-O-, and wherein these variables are further defined in the
Summary above, is reacted with an alcohol, such as methanol, and catalytic acid,
30 such as sulfuric acid, at 0 °C to reflux to obtain the ester of formula I-8 wherein R₁₂ is
methyl and wherein, for example, R₁-X- is benzyl and R₁₀ is hydroxy, and wherein
20 these variables are further defined in the Summary above.

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Scheme J



Scheme J

The compound of formula J-1 wherein the variables correspond to those in the Summary above (see scheme A for its preparation) is reacted with a base such as sodium methoxide, in a protic solvent such as methanol, and methyl acrylate to give the compound of formula J-2 wherein the variables correspond to those in the Summary above. Alternatively, the compound of formula J-1 is prepared using the conditions described in Scheme A for the preparation of the compound of formula A-2 from the compound of formula A-1.

The compound of formula J-2 wherein the variables correspond to those in the Summary above is reacted with a base such as sodium carbonate in a protic solvent or mixed solvents such as methanol/water at 90°C to yield the compound of formula J-3 wherein the variables correspond to those in the Summary above. Alternatively, the compound of formula J-2 is hydrolyzed by the methods mentioned in Protecting Groups in Organic Synthesis, Second Edition, T.W. Greene and P.G.M.

Wuts, John Wiley and Sons, Inc. (1991) to give the corresponding free acid of formula J-3 wherein the variables correspond with those in the Summary above.

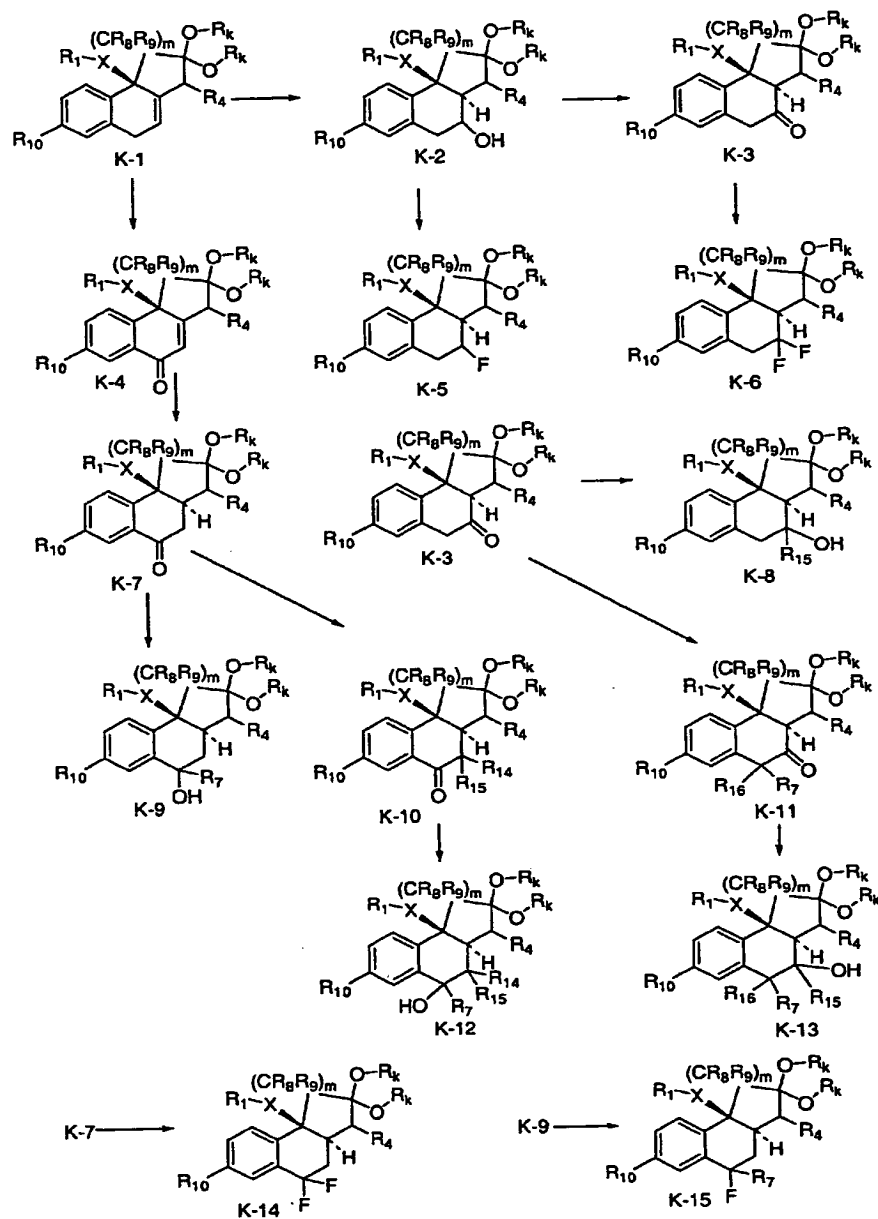
The compound of formula J-3 wherein the variables correspond with those in the Summary above is reacted with a reducing agent, such as sodium borohydride in a protic solvent such as ethanol to give the compound of the formula J-4 wherein the variables are as defined in the Summary above. Alternatively, the compound of the formula J-4 is prepared from the compound of formula J-3 according to other reducing methods described in Modern Synthetic Reactions, Chapters 2-3, pp. 45-227, Herbert O. House, ed., Academic Press, New York (1985).

The compound of formula J-5 wherein the variables are as defined in the Summary above is prepared from the compound of formula J-4 using BBr_3 or BCl_3 and tetrabutylammonium iodide or dimethylboron bromide in an aprotic solvent, such as dichloromethane or toluene, at -78°C to room temperature.

The compound of formula J-6 is prepared from the compound of J-5 using the conditions described in Scheme H for the preparation of the compound of formula H-6 from the compound of formula H-1.

-78-

Scheme K



Scheme K

All compounds in this Scheme can serve as intermediates for Schemes A-3, B, C, F, G, or H.

The compound of formula K-1 (prepared as described in Scheme A-3), wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with a hydroboration reagent, such as BH_3 in THF, in an aprotic solvent, such as THF or dioxane, from 0°C to 60°C and then treated with an oxidizing agent, such as hydrogen peroxide and aqueous sodium hydroxide, from 0°C to 60°C to give the compound of formula K-2. Alternatively, the compound of formula K-2 is prepared from the compound of formula K-1 by other methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 497-498.

The compound of formula K-2, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with a fluorinating agent, such as diethylaminosulfur trifluoride (DAST), in an aprotic solvent, such as diglyme, from 0°C to 60°C, depending on the nature of the solvent used, to give the compound in formula K-5. Alternatively, the compound of formula K-5 is prepared from the compound of formula K-2 by other halogenation methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 353-363.

The compound of formula K-2, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with an oxidizing agent, such as $(nPr)_3NRuO_4$ and N-methylmorpholine-N-oxide, in a solvent, such as dichloromethane, from 0°C to 60°C, depending on the nature of the solvent used, to give the compound in formula K-3. Alternatively, the compound of formula K-3 is prepared from the compound of formula K-2 by other oxidation methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 604-614.

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The compound of formula K-3, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with a fluorinating agent, such as diethylaminosulfur trifluoride (DAST), in an aprotic solvent, such as diglyme, from 0°C to 60°C, depending on the nature of the solvent used, to give the compound in formula K-6. Alternatively, the compound of formula K-6 is prepared from the compound of formula K-3 by other halogenation methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 353-363.

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The compound of formula K-1, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with an oxidizing agent capable of allylic oxidation, such as selenium dioxide (SeO_2) and/or *t*-butyl hydrogen peroxide or chromium trioxide, in a solvent, such as dichloromethane, from 0°C to 60°C, depending on the nature of the solvent used, to give the compound of formula K-4. Alternatively, the compound of formula K-4 is prepared from the compound of formula K-2 by other oxidation methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 592-593.

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The compound of formula K-4, wherein R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and the other variables are as described in the Summary above, is reduced using $Pd(OH)_2$ on carbon or other reagents, such as platinum oxide or rhodium on aluminum oxide (see P.N. Rylander in Hydrogenation Methods, Academic Press, New York, 1985; Herbert O. House in Modern Synthetic Reactions, Chapter 1, pp. 1-45; and John Fried and John A. Edwards in Organic Reactions in Steroid Chemistry, Chapter 3, pp. 111-145) under 15 to 1000 p.s.i (which is about 1 to about 133 atm) H_2 pressure in a solvent, such as toluene, *t*-butyl methyl ether, or ethanol, from 0°C to 60°C, depending on the nature of the solvent used, to give the compound in formula K-7.

The compound of formula K-7, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all

other variables are as described in the Summary above, is treated with a reducing agent, such as sodium borohydride or lithium aluminum hydride, in a solvent, such as methanol or THF, from -78°C to 60°C, depending on the nature of the reductant and/or solvent used, to give the compound in formula K-9, wherein R₇ is hydrogen.

- 5 Alternatively, the compound of formula K-9 is prepared from the compound of formula K-4 by other reduction methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 527-547.
- 10 Alternatively, the compound of formula K-7, wherein R₁₀ is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether, or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with R₇-metal, such as R₇Li, R₇MgBr, or R₇MgCl, wherein R₇ is, for example, alkyl, in an aprotic solvent, such as THF or diethyl ether from -78 °C to 60 °C, depending on the nature of R₇-metal and/or solvent used, to give the compound in formula K-9, wherein
- 15 R₇ is, for example, alkyl.

- The compound of formula K-3, wherein R₁₀ is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with a reducing agent, such as sodium borohydride or lithium aluminum hydride, in a solvent, such as methanol or THF, from -78°C to 60°C, depending on the nature of the reductant and/or solvent used, to give the compound in formula K-8, wherein R₁₅ is hydrogen.
- 20 Alternatively, the compound of formula K-8 is prepared from the compound of formula K-3 by other reduction methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 527-547.
- 25 Alternatively, the compound of formula K-3, wherein R₁₀ is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with R₁₅-metal, such as R₁₅Li, R₁₅MgBr, or R₁₅MgCl, wherein R₁₅ is, for example, alkyl, in an aprotic solvent, such as THF or diethyl ether from -78°C to 60°C, depending on the nature of R₁₅-metal and/or solvent used, to give the compound in formula K-8, wherein R₁₅ is, for example, alkyl.

5 The compound of formula K-7, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for
10 example, lower alkyl or wherein R_k 's taken together are lower alkyl, and all other variables are as described in the Summary above, is converted to its anion with a
5 base, such as sodium hydride, sodium methoxide, or lithium diisopropylamide, in a solvent, such as THF or DMF from -78°C to 60°C , depending on the nature of the
15 base and solvent used. The reaction mixture is treated with an alkylating agent of formula $R_{14}\text{-X}$, wherein R_{14} is, for example, alkyl and X is a leaving group (see
Francis A. Carey, in Advanced Organic Chemistry, Part A, Chapter 5.6 for examples)
10 to give the compound of formula K-10, wherein R_{14} and R_{15} are, for example, alkyl or hydrogen or mixtures thereof.

20 The compound of formula K-3, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for
example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all
25 other variables are as described in the Summary above, is converted to its anion with a base, such as sodium hydride, sodium methoxide, or lithium diisopropylamide, in a
solvent, such as THF or DMF from -78°C to 60°C , depending on the nature of the
30 base and solvent used. The reaction mixture is treated with an alkylating agent of formula $R_7\text{-X}$, wherein R_7 is, for example, alkyl and X is a leaving group (see Francis
A. Carey, in Advanced Organic Chemistry, Part A, Chapter 5.6 for examples) to give
20 the compound of formula K-11, wherein R_7 and R_{16} are, for example, alkyl or hydrogen or mixtures thereof.

35 The compound of formula K-10, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above,
25 R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with a
reducing agent, such as sodium borohydride or lithium aluminum hydride, in a
40 solvent, such as methanol or THF, from -78°C to 60°C , depending on the nature of the reductant and/or solvent used, to give the compound of formula K-12, wherein R_7
30 is hydrogen. Alternatively, the compound of formula K-12 is prepared from the
compound of formula K-10 by other reduction methods known in the art, as
exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH
Publishers Inc. (1989), pp. 527-547. Alternatively, the compound of formula K-10,
50 wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as

described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with R_7 -metal, such as R_7Li , R_7MgBr , or R_7MgCl , wherein R_7 is, for example, alkyl, in an aprotic solvent, such as THF or diethyl ether from $-78^\circ C$ to $60^\circ C$, depending on the nature of R_7 -metal and/or solvent used, to give the compound of formula K-12, wherein R_7 is, for example, alkyl.

The compound of formula K-11, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with a reducing agent, such as sodium borohydride or lithium aluminum hydride, in a solvent, such as methanol or THF, from $-78^\circ C$ to $60^\circ C$, depending on the nature of the reductant and/or solvent used, to give the compound of formula K-13, wherein R_{15} is hydrogen. Alternatively, the compound of formula K-13 is prepared from the compound of formula K-11 by other reduction methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 527-547. Alternatively, the compound of formula K-11, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with R_{15} -metal, such as $R_{15}Li$, $R_{15}MgBr$, or $R_{15}MgCl$, wherein R_{15} is, for example, alkyl, in an aprotic solvent, such as THF or diethyl ether from $-78^\circ C$ to $60^\circ C$, depending on the nature of R_{15} -metal and/or solvent used, to give the compound of formula K-13, wherein R_{15} is, for example, alkyl.

The compound of formula K-7, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with a fluorinating agent, such as diethylaminosulfur trifluoride (DAST), in an aprotic solvent, such as diglyme, from $0^\circ C$ to $60^\circ C$, depending on the nature of the solvent used, to give the compound in formula K-14. Alternatively, the compound of formula K-14 is prepared from the compound of formula K-7 by other halogenation methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH Publishers Inc. (1989), pp. 353-363.

5 The compound of formula K-9, wherein R_{10} is halogen, hydrogen, carboxylate, methyl ether, or benzyl ether or is as described in the Summary above, R_k is, for
10 example, lower alkyl or wherein R_k 's taken together are cyclic lower alkyl, and all other variables are as described in the Summary above, is treated with a fluorinating
5 agent, such as diethylaminosulfur trifluoride (DAST), in an aprotic solvent, such as diglyme, from 0°C to 60°C, depending on the nature of the solvent used, to give the
15 compound in formula K-15. Alternatively, the compound of formula K-15 is prepared from the compound of formula K-9 by other halogenation methods known in the art, as exemplified in Comprehensive Organic Transformations, R.C. Larock, VCH
10 Publishers Inc. (1989), pp. 353-363.

20 Some of the preparation methods useful for the preparation of the compounds described herein may require protection of remote functionality (e.g., primary amine, secondary amine, carboxyl in Formula I precursors). The need for
25 such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. The need for such protection is readily
15 determined by one skilled in the art. The use of such protection/deprotection methods is also within the skill in the art. For a general description of protecting groups and their use, see T.W. Greene, Protective Groups in Organic Synthesis, John Wiley &
30 Sons, New York, 1991.

20 The subject invention also includes isotopically-labelled compounds, which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the
35 atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{13}C ,
25 ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said
40 compounds and of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain
30 isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug
45 and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , can afford
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5 certain therapeutic advantages resulting from greater metabolic stability, for example
increased *in vivo* half-life or reduced dosage requirements and, hence, may be
10 preferred in some circumstances. Isotopically labelled compounds of Formula I of
this invention and prodrugs thereof can generally be prepared by carrying out the
5 procedures disclosed in the Schemes and/or in the Examples below, by substituting a
readily available isotopically labelled reagent for a non-isotopically labelled reagent.

15 Any of the compounds and prodrugs of the present invention can be
synthesized as pharmaceutically acceptable salts for incorporation into various
pharmaceutical compositions. As used herein, pharmaceutically acceptable salts
10 include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric,
sulfuric, sulfonic, citric, camphoric, maleic, acetic, lactic, nicotinic, nitric, succinic,
20 phosphoric, malonic, malic, salicylic, phenylacetic, stearic, palmitic, pyridine,
ammonium, piperazine, diethylamine, nicotinamide, formic, fumaric, urea, sodium,
potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino,
25 15 methanesulfonic, picric, p-toluenesulfonic, naphthalenesulfonic, tartaric, triethylamino,
dimethylamino, and tris(hydroxymethyl)aminomethane. Additional pharmaceutically
acceptable salts would be apparent to one of ordinary skill in the art. Where more
than one basic moiety exists, the expression includes multiple salts (e.g., di-salt).

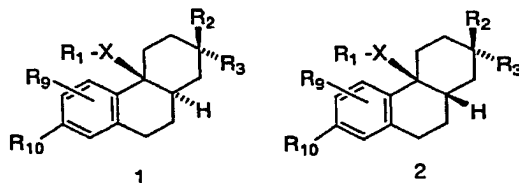
30 Some of the compounds of this invention are acidic and they form a salt with
20 a pharmaceutically acceptable cation. Some of the compounds of this invention are
basic and they form a salt with a pharmaceutically acceptable anion. All such salts,
including di-salts, are within the scope of this invention and they can be prepared by
35 conventional methods. They can be prepared simply by contacting the acidic and
basic entities, in either an aqueous, non-aqueous or partially aqueous medium. For
25 example, the mesylate salt is prepared by reacting the free base form of the
compound of Formula I with methanesulfonic acid under standard conditions.
40 Likewise, the hydrochloride salt is prepared by reacting the free base form of the
compound of Formula I with hydrochloric acid under standard conditions. The salts
are recovered either by filtration, by precipitation with a non-solvent followed by
30 filtration, by evaporation of the solvent, or, in the case of aqueous solutions, by
45 lyophilization, as appropriate.

In addition, when the compounds and prodrugs of the present invention form
hydrates or solvates, they are also within the scope of the present invention.

The compounds and prodrugs of the present invention also includes racemates, stereoisomers and mixtures of these compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

For instance, the compounds of the present invention have asymmetric carbon atoms and are therefore enantiomers or diastereomers. Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical/chemical differences by methods known in the art, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomers, enantiomers and mixtures thereof are considered as part of this invention.

The following configurations of the compounds of the present invention (as represented by simplified structures) are preferred, with the first configuration being more preferred:



Also, the compounds and prodrugs of the present invention can exist in several tautomeric forms, including the enol form, the keto form and mixtures thereof. All such tautomeric forms are included within the scope of the present invention.

The GR agonists, partial agonists and antagonists of the present invention can be used to influence the basic, life sustaining systems of the body, including carbohydrate, protein and lipid metabolism, electrolyte and water balance, and the functions of the cardiovascular, kidney, central nervous, immune, skeletal muscle and other organ and tissue systems. In this regard, GR modulators are used for the treatment of diseases associated with an excess or a deficiency of glucocorticoids in the body. As such, they may be used to treat the following: obesity, diabetes,

cardiovascular disease, hypertension, Syndrome X, depression, anxiety, glaucoma, human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), neurodegeneration (for example, Alzheimer's and Parkinson's), cognition enhancement, Cushing's Syndrome, Addison's Disease, osteoporosis, frailty, inflammatory diseases (such as osteoarthritis, rheumatoid arthritis, asthma and rhinitis), tests of adrenal function, viral infection, immunodeficiency, immunomodulation, autoimmune diseases, allergies, wound healing, compulsive behavior, multi-drug resistance, addiction, psychosis, anorexia, cachexia, post-traumatic stress syndrome, post-surgical bone fracture, medical catabolism and prevention of muscle frailty.

The compounds of the present invention, isomers, prodrugs and pharmaceutically acceptable salts thereof are useful to induce weight loss in mammals needing or desiring to lose weight. While not intending to limit the present invention to a specific mechanism of action, the compounds of the present invention, isomers, prodrugs and salts thereof are able to induce weight loss by a variety of mechanisms, such as appetite suppression, decreasing food intake, and stimulation of the metabolic rate in peripheral tissue, thereby increasing energy expenditure. In addition, the compounds of the present invention, isomers, prodrugs and salts thereof are useful to induce a more favorable partitioning of nutrients from fat to muscle tissue in mammals. Thus, while not necessarily resulting in weight loss, this increase in muscle mass may be useful in preventing or treating diseases, such as obesity and frailty.

In addition, the compounds of the present invention, isomers, prodrugs and pharmaceutically acceptable salts thereof may also be useful to increase lean meat deposition, improve lean meat to fat ratio, and trim unwanted fat from non-human animals, as described further below.

It will be understood by those skilled in the art that while the compounds, isomers, prodrugs and pharmaceutically acceptable salts thereof of the present invention will typically be employed as selective agonists, partial agonists or antagonists, there may be instances where a compound with a mixed steroid receptor profile is preferred.

Furthermore, it will be understood by those skilled in the art that the compounds, isomers, prodrugs and pharmaceutically acceptable salts thereof of the present invention, including pharmaceutical compositions and formulations containing

5 these compounds, isomers, prodrugs and salts can be used in a wide variety of
combination therapies to treat the conditions and diseases described above. Thus,
10 the compounds, isomers, prodrugs and pharmaceutically acceptable salts thereof of
the present invention can be used in conjunction with other pharmaceutical agents for
5 the treatment of the disease/conditions described herein. For example, they may be
used in combination with pharmaceutical agents that treat obesity, diabetes,
15 inflammatory disease, immunodeficiency, hypertension, cardiovascular disease, viral
infection, HIV, Alzheimer's disease, Parkinson's disease, anxiety, depression, or
psychosis. In combination therapy treatment, both the compounds, isomers, prodrugs
10 and pharmaceutically acceptable salts thereof of this invention and the other drug
therapies are administered to mammals (e.g., humans, male or female) by
20 conventional methods.

For instance, glucocorticoid receptor agonists are efficacious agents for the
treatment of various inflammatory diseases; however, treatment is often
25 accompanied by undesirable side effects. These side effects include, but are not
limited to, the following examples: metabolic effects, weight gain, muscle wasting,
decalcification of the skeleton, osteoporosis, thinning of the skin and thinning of the
30 skeleton. However, according to the present invention, glucocorticoid receptor
modulators may be used in combination with glucocorticoid receptor agonists to block
20 some of these side effects, without inhibiting the efficacy of the treatment. Thus, any
glucocorticoid receptor agonist may be used as the second compound in the
combination aspect of the present invention. This combination includes the treatment
35 of various inflammatory diseases, such as arthritis (osteo and rheumatoid), asthma,
rhinitis, or immunomodulation. Examples of glucocorticoid receptor modulators
25 include those known in the art (many of which are described above) as well as the
novel compounds of formula I of the present invention. More particularly, examples
40 of glucocorticoid receptor modulators known in the art include, but are not limited to,
certain nonsteroidal compounds, such as 5H-chromeno[3,4-f]quinolines, which are
selective modulators of steroid receptors, as disclosed in U.S. Patent No. 5,696,127;
30 and certain steroid compounds substituted at position 10, which possess
antiglucocorticoid activity, and some of which have glucocorticoid activity, as
disclosed in Published European Patent Application 0 188 396, published 23 July
1986. Examples of glucocorticoid receptor agonists include those known in the art,
50 such as prednisone (17,21-dihydroxypregnane-1,4-diene-3,11,20-trione),

5 prednylidene ((11 β)-11,17,21-trihydroxy-16-methylenepregna-1,4-diene-3, 20-dione),
prednisolone ((11 β)-11,17,21-trihydroxypregna-1,4-diene-3, 20-dione), cortisone
10 (17 α ,21-dihydroxy-4-pregnene-3,11,20-trione), dexamethasone ((11 β , 16 α)-9-fluoro-
11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione), and hydrocortisone
5 (11 β ,17 α ,21-trihydroxypregn-4-ene-3, 20-dione). These compounds, which are
glucocorticoid receptor agonists, will generally be administered in the form of a
15 dosage unit at a therapeutically effective amount of such compound. For example,
prednisone or an equivalent drug may be administered from about 5 to about 80 mg,
depending on the condition; hydrocortisone may be administered from about 100 to
20 about 400 mg, depending on the condition; and dexamethasone may be
administered from about 4 to about 16 mg, depending on the condition. These doses
are typically administered once to twice daily, and for maintenance purposes,
sometimes on alternate days.

25 For the treatment of Alzheimer's disease, any cholinomimetic drug, such as
15 donepezil, may be used as the second compound in the combination aspect of this
invention.

30 For the treatment of Parkinson's disease, any anti-Parkinson's drug, such as
L-dopa, bromocriptine, or selegiline, may be used as the second compound in the
combination aspect of this invention.

20 For the treatment of anxiety, any antianxiolytic drug, such as benzodiazepine,
valium, or librium, may be used as the second compound in the combination aspect
of this invention.

35 For the treatment of depression, any tricyclic antidepressant such as,
desipramine, or any selective serotonin reuptake inhibitor (SSRI's), such as sertraline
25 hydrochloride and fluoxetine hydrochloride, may be used as the second compound in
the combination aspect of this invention.

40 For the treatment of psychosis, any typical or atypical antipsychotic drug, such
as haloperidol or clozapine may be used as the second compound in the combination
aspect of this invention.

45 30 Any aldose reductase inhibitor may be used as the second compound in the
combination aspect of this invention. The term aldose reductase inhibitor refers to a
compound which inhibits the bioconversion of glucose to sorbitol catalyzed by the
enzyme aldose reductase. Such inhibition is readily determined by those skilled in
50 the art according to standard assays (J. Malone, Diabetes, 29:861-864, 1980, "Red

Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose reductase inhibitors are described and referenced below; however other aldose reductase inhibitors will be known to those skilled in the art. Examples of aldose reductase inhibitors useful in the compositions and methods of this invention include, for example, zopolrestat, and other such compounds as disclosed and described in PCT/IB99/00206, filed 5 February 1999 (the disclosure of which is hereby incorporated by reference), and assigned to the assignee hereof.

Any glycogen phosphorylase inhibitor may be used as the second compound in the combination aspect of this invention. The term glycogen phosphorylase inhibitor refers to any substance or agent or any combination of substances and/or agents which reduces, retards or eliminates the enzymatic action of glycogen phosphorylase. The currently known enzymatic action of glycogen phosphorylase is the degradation of glycogen by catalysis of the reversible reaction of a glycogen macromolecule and inorganic phosphate to glucose-1-phosphate and a glycogen macromolecule which is one glucosyl residue shorter than the original glycogen macromolecule (forward direction of glycogenolysis). Such actions are readily determined by those skilled in the art according to standard assays (e.g., as described in PCT/IB99/00206, filed 5 February 1999). A variety of these compounds are described in the following published international patent applications: WO 96/39384, published 12 December 1996, and WO 96/39385, published 12 December 1996; and in the following filed international patent application: PCT/IB99/00206, filed 5 February 1999; the disclosures of all of these applications are hereby incorporated by reference herein.

Any sorbitol dehydrogenase inhibitor may be used as the second compound in the combination aspect of this invention. The term sorbitol dehydrogenase inhibitor refers to a compound which inhibits the enzyme sorbitol dehydrogenase, which catalyzes the oxidation of sorbitol to fructose. Such inhibition is readily determined by those skilled in the art according to standard assays (as described in U.S. Patent No. 5,728,704 and references cited therein). A variety of these compounds are described and referenced below; however other sorbitol dehydrogenase inhibitors will be known to those skilled in the art. U.S. Pat. No. 5,728,704 (the disclosure of which is hereby incorporated by reference) discloses substituted pyrimidines which inhibit sorbitol dehydrogenase, lower fructose levels, and/or treat or prevent diabetic complications,

5 such as diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, diabetic microangiopathy and diabetic macroangiopathy.

10 Any known, commercially marketed antidiabetic compound may be used as the second compound in the combination aspect of this invention. A variety of such compounds are described and referenced below; however other such compounds will be known to those skilled in the art. Examples of such compounds useful in the compositions and methods of this invention include, for example, insulin, metformin, troglitazone (REZULIN®) and sulfonylureas, such as glipizide (GLUCOTROL®), glyburide (GLYNASE®, MICRONASE®) and chlorpropamide (DIABINASE®).

15 Any β -adrenergic agonist may be used as the second compound in the combination aspect of this invention. β -Adrenergic agents have been categorized into β_1 , β_2 , and β_3 subtypes. Agonists of β -receptors promote the activation of adenylyl cyclase. Activation of β_1 receptors invokes increases in heart rate. Activation of β_2 receptors induces relaxation of smooth muscle tissue which produces a drop in blood pressure and the onset of skeletal muscle tremors. Activation of β_3 receptors is known to stimulate lipolysis, which is the breakdown of adipose tissue triglycerides to glycerol and fatty acids. Activation of β_3 receptors also stimulates the metabolic rate, thereby increasing energy expenditure. Accordingly, activation of β_3 receptors promotes the loss of fat mass. Compounds that stimulate β receptors are therefore useful as anti-obesity agents. Compounds which are β_3 -receptors agonists have hypoglycemic and/or anti-diabetic activity. Such activity is readily determined by those skilled in the art according to standard assays (International Patent Application, Publication No. WO 96/35671). Several compounds are described and referenced below; however, other β -adrenergic agonists will be known to those skilled in the art.

25 International Patent Application, Publication No. WO 96/35671 (the disclosure of which is incorporated herein by reference) discloses compounds, such as substituted aminopyridines, which are β -adrenergic agonists. International Patent Application, Publication No. 93/16189 (the disclosure of which is incorporated herein by reference) discloses the use of selective β_3 receptor agonists in combination with compounds which modify eating behavior for the treatment of obesity.

30 Any thyromimetic antiobesity agent may be used as the second compound in the combination aspect of this invention. These compounds are tissue selective thyroid hormone agonists. These compounds are able to induce weight loss by

mechanisms other than appetite suppression, e.g., through stimulation of the metabolic rate in peripheral tissue, which, in turn, produces weight loss. Such metabolic effect is readily measured by those skilled in the art according to standard assays. A variety of these compounds are described and referenced below; however, other thyromimetic antiobesity agents will be known to those skilled in the art. It is well known to one of ordinary skill in the art that selectivity of thermogenic effect is an important requirement for a useful therapeutic agent in the treatment of, for example, obesity and related conditions.

Any eating behavior modifying compound may be used as the second compound of this invention. Compounds which modify eating behavior include anorectic agents, which are compounds which diminish the appetite. Such classes of anorectic agents are well known to one of ordinary skill in the art. A variety of these compounds are described in and referenced below; however, other anorectic agents will be known to those skilled in the art. Also, the following are antiobesity agents: phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, a Neuropeptide Y (hereinafter also referred to as "NPY") antagonist, a cholecystokinin-A (hereinafter referred to as CCK-A) agonist, a monoamine reuptake inhibitor (such as sibutramine), a sympathomimetic agent, a serotonergic agent (such as dexfenfluramine or fenfluramine), a dopamine agonist (such as bromocriptine), a melanocyte-stimulating hormone receptor agonist or mimetic, a melanocyte-stimulating hormone analog, a cannabinoid receptor antagonist, a melanin concentrating hormone antagonist, the OB protein (hereinafter referred to as "leptin"), a leptin analog, a galanin antagonist or a GI lipase inhibitor or decreaser (such as orlistat). Other antiobesity agents include phosphatase 1B inhibitors, bombesin agonists, dehydroepiandrosterone or analogs thereof, glucocorticoid receptor modulators, orexin receptor antagonists, urocortin binding protein antagonists or glucagon-like peptide-1 (insulinotropin) agonists. A particularly preferred monoamine reuptake inhibitor is sibutramine, which can be prepared as disclosed in U.S. Patent No. 4,929,629, the disclosure of which is incorporated herein by reference. Preferred serotonergic agents include fenfluramine and dexfenfluramine, which can be prepared as disclosed in U.S. Patent No. 3,198,834, the disclosure of which is incorporated herein by reference. A particularly preferred dopamine agonist is bromocriptine, which can be prepared as disclosed in U.S. Patent Nos. 3,752,814 and 3,752,888, the disclosures of which are incorporated herein by reference.

Another preferred anorectic agent is phentermine, which can be prepared as disclosed in U.S. Patent No. 2,408,345, the disclosure of which is incorporated herein by reference.

Any NPY receptor antagonist may be used as the second component in the combination aspect of this invention. The term NPY receptor antagonist refers to compounds which interact with NPY receptors and inhibit the activity of neuropeptide Y at those receptors and thus are useful in treating disorders associated with neuropeptide Y, such as feeding disorders, including obesity. Such inhibition is readily determined by those skilled in the art according to standard assays (such as those described in International Patent Application, Publication No. WO 99/07703). In addition, the compounds described and referenced below are NPY receptor antagonists; however, other NPY receptor antagonists will also be known to those skilled in the art. International Patent Application, Publication No. WO 99/07703 (the disclosure of which is hereby incorporated by reference) discloses certain 4-aminopyrrole (3,2-d) pyrimidines as neuropeptide Y receptor antagonists. International patent application, Publication No. WO 96/14307, published 17 May 1996; International patent application, Publication No. WO 96/40660, published 19 December 1996; International patent application, Publication No. WO 98/03492; International patent application, Publication No. WO 98/03494; International patent application, Publication No. WO 98/03493; International patent application, Publication No. WO 96/14307, published 17 May 1996; International patent application, Publication No. WO 96/40660, published 19 December 1996; (the disclosures of which are hereby incorporated by reference) disclose additional compounds, such as substituted benzylamine derivatives, which are useful as neuropeptide Y specific ligands.

In combination therapy treatment, both the compounds of this invention and the other drug therapies are administered to mammals (e.g., humans, male or female) by conventional methods. As recognized by those skilled in the art, the therapeutically effective amounts of the compounds of this invention and the other drug therapies to be administered to a patient in combination therapy treatment will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

For example, the second compound of this invention, when administered to a mammal, is dosed at a range between about 0.01 to about 50 mg/kg/day body

weight, preferably about 0.1 mg/kg/day to about 10 mg/kg/day body weight, administered singly or as a divided dose. Particularly, when the second compound of this invention is (1) sibutramine, the dosage of sibutramine is about 0.01 mg/kg/day to about 30 mg/kg/day body weight, preferably about 0.1 mg/kg/day to about 1 mg/kg/day body weight; (2) dexfenfluramine, the dosage of dexfenfluramine is about 0.01 mg/kg/day to about 30 mg/kg/day body weight, preferably about 0.1 mg/kg/day to about 1 mg/kg/day body weight; (3) bromocriptine, the dosage of bromocriptine is about 0.01 to about 10 mg/kg/day body weight, preferably 0.1 mg/kg/day to about 10 mg/kg/day body weight; (4) phentermine, the dosage of phentermine is about 0.01 mg/kg/day to about 10 mg/kg/day, preferably about 0.1 mg/kg/day to about 1 mg/kg/day body weight. Also, for example, as noted above, an amount of an aldose reductase inhibitor that is effective for the activities of this invention may be used as the second compound of this invention. Typically, an effective dosage for aldose reductase inhibitors for this invention is in the range of about 0.1 mg/kg/day to about 100 mg/kg/day in single or divided doses, preferably about 0.1 mg/kg/day to about 20 mg/kg/day in single or divided doses.

As noted above, the compounds, isomers, prodrugs and pharmaceutically acceptable salts of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier, vehicle or diluent to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and more preferably, in human, patients. The particular carrier, vehicle or diluent employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired, for example, intravenous, oral, topical, suppository or parenteral. Also, the compounds, isomers, prodrugs and salts thereof of this invention can be administered individually or together in any conventional dosage form, such as an oral, parenteral, rectal or transdermal dosage form.

For oral administration a pharmaceutical composition can take the form of solutions, suspensions, tablets, pills, capsules, powders, and the like. Tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate are employed along with various disintegrants such as starch and preferably potato or tapioca starch and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are

5 often very useful for tableting purposes. Solid compositions of a similar type are also
employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this
10 connection also include lactose or milk sugar as well as high molecular weight
polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral
5 administration, the compounds, prodrugs and pharmaceutically acceptable salts
thereof of this invention can be combined with various sweetening agents, flavoring
15 agents, coloring agents, emulsifying agents and/or suspending agents, as well as
such diluents as water, ethanol, propylene glycol, glycerin and various like
combinations thereof.

10 Due to their ease of administration, tablets and capsules represent the most
advantageous oral dosage form for the pharmaceutical compositions of the present
20 invention.

For purposes of parenteral administration, solutions in sesame or peanut oil
or in aqueous propylene glycol can be employed, as well as sterile aqueous solutions
25 15 of the corresponding water-soluble salts. Such aqueous solutions may be suitably
buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient
saline or glucose. These aqueous solutions are especially suitable for intravenous,
intramuscular, subcutaneous and intraperitoneal injection purposes. In this
30 connection, the sterile aqueous media employed are all readily obtainable by
20 standard techniques well-known to those skilled in the art.

For purposes of transdermal (e.g., topical) administration, dilute sterile,
aqueous or partially aqueous solutions (usually in about 0.1% to 5% concentration),
35 otherwise similar to the above parenteral solutions, are prepared.

For topical administration, the compounds of the present invention may be
25 formulated using bland, moisturizing bases, such as ointments or creams. Examples
of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin,
40 and water in oil emulsions.

Methods of preparing various pharmaceutical compositions with a certain
amount of active ingredient are known, or will be apparent in light of this disclosure, to
45 30 those skilled in this art. For examples of methods of preparing pharmaceutical
compositions, see Remington's Pharmaceutical Sciences, Mack Publishing
Company, Easter, Pa., 15th Edition (1975).

The pharmaceutical compositions and compounds, isomers, prodrugs and
50 pharmaceutically acceptable salts thereof of the present invention will generally be

5 administered in the form of a dosage unit (e.g., tablet, capsule, etc.) at a
therapeutically effective amount of such compound, prodrug or salt thereof from
10 about 0.1 $\mu\text{g/kg}$ of body weight to about 500 mg/kg of body weight, more particularly
from about 1 $\mu\text{g/kg}$ to about 250 mg/kg, and most particularly from about 2 $\mu\text{g/kg}$ to
5 about 100 mg/kg. More preferably, a compound of the present invention will be
administered at an amount of about 0.1 mg/kg to about 500 mg/kg of body weight,
15 and most preferably from about 0.1 mg/kg to about 50 mg/kg of body weight. As
recognized by those skilled in the art, the particular quantity of pharmaceutical
composition according to the present invention administered to a patient will depend
20 upon a number of factors, including, without limitation, the biological activity desired,
the condition of the patient, and tolerance for the drug.

Since the present invention has an aspect that relates to the treatment of the
disease/conditions described herein with a combination of active ingredients which
may be administered separately, the invention also relates to combining separate
25 pharmaceutical compositions in kit form. The kit comprises two separate
pharmaceutical compositions: a compound of formula I, an isomer thereof, a prodrug
thereof or a salt of such compound, isomer or prodrug and a second compound as
described above. The kit comprises a container, such as a divided bottle or a divided
30 foil packet. Typically the kit comprises directions for the administration of the separate
components. The kit form is particularly advantageous when the separate
components are preferably administered in different dosage forms (e.g., oral and
parenteral), are administered at different dosage intervals, or when titration of the
35 individual components of the combination is desired by the prescribing physician.

An example of such a kit is a so-called blister pack. Blister packs are well
25 known in the packaging industry and are being widely used for the packaging of
pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs
generally consist of a sheet of relatively stiff material covered with a foil of a
preferably transparent plastic material. During the packaging process, recesses are
40 formed in the plastic foil. The recesses have the size and shape of the tablets or
capsules to be packed. Next, the tablets or capsules are placed in the recesses and
the sheet of relatively stiff material is sealed against the plastic foil at the face of the
45 foil which is opposite from the direction in which the recesses were formed. As a
result, the tablets or capsules are sealed in the recesses between the plastic foil and
the sheet. Preferably, the strength of the sheet is such that the tablets or capsules
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can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

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It may be desirable to provide a memory aid on the kit, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, e.g., as follows "First Week, Monday, Tuesday, ...etc.... Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of formula I compound (or an isomer, prodrug or pharmaceutically acceptable salt thereof) can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

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In another specific embodiment of the invention, a dispenser designed to dispense the daily doses one at a time in the order of their intended use is provided. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

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The following paragraphs describe exemplary formulations, dosages etc. useful for non-human animals. The administration of compounds of this invention can be effected orally or non-orally, for example by injection. An amount of a compound of formula I, an isomer, prodrug or pharmaceutically acceptable salt thereof, is administered such that a therapeutically effective dose is received, generally a daily dose which, when administered orally to an animal is usually between 0.01 and 500 mg/kg of body weight, preferably between 0.1 and 50 mg/kg of body weight. Conveniently, the medication can be carried in the drinking water so that a therapeutic dosage of the agent is ingested with the daily water supply. The agent can be directly metered into drinking water, preferably in the form of a liquid, water-soluble concentrate (such as an aqueous solution of a water soluble salt).

Conveniently, the active ingredient can also be added directly to the feed, as such, or in the form of an animal feed supplement, also referred to as a premix or concentrate.

A premix or concentrate of therapeutic agent in a carrier is more commonly employed for the inclusion of the agent in the feed. Suitable carriers are liquid or solid, as desired, such as water, various meals such as alfalfa meal, soybean meal, cottonseed oil meal, linseed oil meal, corn cob meal and corn meal, molasses, urea, bone meal, and mineral mixes such as are commonly employed in poultry feeds. A particularly effective carrier is the respective animal feed itself; that is, a small portion of such feed. The carrier facilitates uniform distribution of the active materials in the finished feed with which the premix is blended. It is important that the compound be thoroughly blended into the premix and, subsequently, the feed. In this respect, the agent may be dispersed or dissolved in a suitable oily vehicle such as soybean oil, corn oil, cottonseed oil, and the like, or in a volatile organic solvent and then blended with the carrier. It will be appreciated that the proportions of active material in the concentrate are capable of wide variation since the amount of agent in the finished feed may be adjusted by blending the appropriate proportion of premix with the feed to obtain a desired level of therapeutic agent.

High potency concentrates may be blended by the feed manufacturer with proteinaceous carrier such as soybean oil meal and other meals, as described above, to produce concentrated supplements which are suitable for direct feeding to animals. In such instances, the animals are permitted to consume the usual diet.

Alternatively, such concentrated supplements may be added directly to the feed to produce a nutritionally balanced, finished feed containing a therapeutically effective level of a compound according to the invention. The mixtures are thoroughly blended by standard procedures, such as in a twin shell blender, to ensure homogeneity.

If the supplement is used as a top dressing for the feed, it likewise helps to ensure uniformity of distribution of the active material across the top of the dressed feed.

The present invention has several advantageous veterinary features. For the pet owner or veterinarian who wishes to increase leanness and trim unwanted fat from pet animals, the present invention provides the means by which this can be accomplished. For poultry and swine raisers, using the method of the present invention yields leaner animals which command higher prices from the meat industry.

Drinking water and feed effective for increasing lean meat deposition and for improving lean meat to fat ratio are generally prepared by mixing a compound of the invention with a sufficient amount of animal feed to provide from about 10^{-3} to 500 ppm of the compound in the feed or water.

The preferred medicated swine, cattle, sheep and goat feed generally contain from 1 to 400 grams of active ingredient per ton of feed, the optimum amount for these animals usually being about 50 to 300 grams per ton of feed.

The preferred feed of domestic pets, such as cats and dogs, usually contain about 1 to 400 grams and preferably 10 to 400 grams of active ingredient per ton of feed.

For parenteral administration in animals, the compounds of the present invention may be prepared in the form of a paste or a pellet and administered as an implant, usually under the skin of the head or ear of the animal in which increase in lean meat deposition and improvement in lean meat to fat ratio is sought.

In general, parenteral administration involves injection of a sufficient amount of a compound of the present invention to provide the animal with 0.01 to 500 mg/kg/day of body weight of the active ingredient. The preferred dosage for poultry, swine, cattle, sheep, goats and domestic pets is in the range of from 0.1 to 50 mg/kg/day of body weight of active ingredient.

Paste formulations can be prepared by dispersing the active compound in a pharmaceutically acceptable oil such as peanut oil, sesame oil, corn oil or the like.

Pellets containing an effective amount of a compound of the present invention can be prepared by admixing a compound of the present invention with a diluent such as carbowax, camuba wax, and the like, and a lubricant, such as magnesium or calcium stearate, can be added to improve the pelleting process.

It is, of course, recognized that more than one pellet may be administered to an animal to achieve the desired dose level which will provide the increase in lean meat deposition and improvement in lean meat to fat ratio desired. Moreover, it has been found that implants may also be made periodically during the animal treatment period in order to maintain the proper drug level in the animal's body.

The activity of the compounds of the present invention are demonstrated by one or more of the assays described below:

The following is a description of an assay for the identification of glucocorticoid receptor antagonists/agonists: HeLa cells containing endogenous

5 human glucocorticoid receptors are transfected with a 3xGRE-luciferase plasmid
generated by standard procedures and a plasmid conferring neomycin resistance.
10 Novel glucocorticoid responsive cell lines are generated and characterized. One
such cell line designated HeLa-GRE9 is used for determining the activity of
5 compounds at the glucocorticoid receptor. Cells are maintained in charcoal-stripped
serum and transferred to 96-well microtiter plates one day prior to treatment with
15 various concentrations (10^{-12} to 10^{-5}) of test compounds in the absence and presence
of known glucocorticoid receptor agonists (i.e., dexamethasone, hydrocortisone) for
up to 24 hours. Treatments are performed in triplicate. Cell lysates are prepared and
10 luciferase activity is determined using a luminometer. Agonist activity is assessed by
comparing the luciferase activity from cells treated with test compound to cells treated
20 with the agonist dexamethasone. Antagonist activity is assessed by comparing the
luciferase activity of an EC_{50} concentration of dexamethasone in the absence and
presence of test compound. The EC_{50} (concentration that produced 50% of the
25 maximal response) for dexamethasone is calculated from dose response curves.

The following is a description of an assay for determining the competitive
inhibition binding of the Human Type II Glucocorticoid receptor expressed in Sf9 cells:

30 Binding protocol: Compounds are tested in a binding displacement assay
using human glucocorticoid receptor expressed in Sf9 cells with 3H -dexamethasone
as the ligand. Human glucocorticoid receptor is expressed in Sf9 cells as described in
20 Mol. Endocrinology 4: 209, 1990. Pellets containing Sf9 cells expressing the human
GR receptor from 1L vials are lysed with 40 μ l of 20mM AEBSF stock (Calbiochem,
35 LaJolla, CA) containing 50 mg/ml leupeptin and 40 ml of homogenization buffer is
added. The assay is carried out in 96-well polypropylene plates in a final volume of
25 130 μ l containing 200 μ g Sf9 lysate protein, 6.9 nM 3H -dexamethasone (Amersham,
Arlington Heights, IL) in presence of test compounds, test compound vehicle (for total
40 counts) or excess dexamethasone (7 μ M non-radioactive, to determine non-specific
binding) in an appropriate volume of assay buffer. All compounds are tested at 6
concentrations in duplicate (concentration range 0.1-30 nM or 3-1000 nM). Test
30 compounds are diluted from a 25 mM stock in 100% DMSO with 70%EtOH and
added in a volume of 2 μ l. Once all additions are made the plates are shaken,
45 sealed with sealing tape and incubated at 4 $^{\circ}$ C overnight.

After the overnight incubation, unbound counts are removed with dextran
50 coated charcoal as follows: 75 μ l of dextran coated charcoal (5.0 g activated

5 charcoal, 0.5 g dextran adjusted to volume of 100 ml with assay buffer) is added,
plates are shaken and incubated for five minutes at 4 °C. Plates are then centrifuged
10 in a refrigerated benchtop centrifuge at top speed for 15 minutes. 100 µl of the
supernatant from each well is placed into a 96-well PET plate with 200 µl of
5 scintillation cocktail and counted on a beta counter (1450 MicroBetaTrilux, from
Wallac, Turku, Finland).

15 Data analysis: After subtracting non-specific binding, counts bound are
expressed as % of total counts. The concentration response for test compounds are
fitted to a sigmoidal curve to determine the IC₅₀ (concentration of compound that
10 displaces 50% of the bound counts).

20 Reagents: Assay Buffer: 2.0 ml 1M Tris, 0.2 ml 0.5mM EDTA, 77.1 mg DTT,
0.243 g sodium molybdate in a volume of 100 ml water; Homogenization buffer: 2.0
ml 0.5 M K₂HPO₄ (pH 7.6), 20 µl 0.5 M EDTA (pH 8.0), 77.1 mg DTT, 0.486 g
sodium molybdate in a volume of 100 ml water.

25 15 The following is a description of an assay for determining receptor selectivity:
T47D cells from ATCC containing endogenous human progesterone and
mineralocorticoid receptors are transiently transfected with a 3xGRE-luciferase using
Lipofectamine Plus (GIBCO-DRL, Gaithersburg, MD). Twenty-four hours post-
30 transfection cells are maintained in charcoal-stripped serum and transferred to 96-
well microtiter plates. The next day cells are treated with various concentrations (10⁻¹²
20 to 10⁻⁵) of test compounds in the absence and presence of a known progesterone
receptor agonist (progesterone) and a known mineralocorticoid receptor agonist
(aldosterone) for up to 24 hours. Treatments are performed in triplicate. Cell lysates
35 are prepared and luciferase activity is determined using a luminometer. Agonist
activity is assessed by comparing the luciferase activity from cells treated with
25 compound alone to cells treated with either the agonist progesterone or aldosterone.
Antagonist activity is assessed by comparing the luciferase activity of an EC₅₀
40 concentration of progesterone or aldosterone in the absence and presence of
compound. The EC₅₀ (concentration that produced 50% of maximal response) for
30 progesterone and aldosterone is calculated from dose response curves.

45 The following is a description of an assay for determining anti-diabetes and
anti-obesity activity: The obese, diabetic ob/ob mouse is used to assess the anti-
diabetes and anti-obesity activity of the compounds. Six to 10 week old ob/ob male
50 mice (Jackson Labs, Bar Harbor, Maine) are dosed with test compound for 2 to 10

5 days. Plasma glucose levels are determined by measuring glucose from samples
obtained by orbital bleeding. Glucose is quantitated using an Abbott Autoanalyzer
(Abbott, Inc., Abbott Park, IL). Food intake is monitored on a daily basis by
10 differential weighing.

5 The following is a description of an assay for determining the ability of a
compound to inhibit glucocorticoid agonist induction of liver tyrosine amino
transferase (TAT) activity in conscious rats:

15 Animals: Male Sprague Dawley rats (from Charles River, Wilmington MA)
(adrenal-intact or adrenalectomized at least one week prior to the screen) b.w. 90g
10 are used. The rats are housed under standard conditions for 7-10d prior to use in the
screen.

20 Experimental protocol: Rats (usually 3 per treatment group) are dosed with
test compound, vehicle or positive control (Ru486) either i.p., p.o., s.c. or i.v. (tail
vein). The dosing vehicle for the test compounds is typically one of the following:
25 100% PEG 400, 0.25% methyl cellulose in water, 70% ethanol or 0.1 N HCl and the
compounds are tested at doses ranging from 10 to 125 mg/kg. The compounds are
dosed in a volume of 1.0 ml/ 100 g body weight (for p.o.) or 0.1 ml/100g body weight
for other routes of administration. Ten minutes after the administration of the test
30 compound, the rats are injected with dexamethasone (0.03 mg/kg i.p. in a volume of
0.1 ml/ 100g) or vehicle. To prepare the dexamethasone dosing solution,
20 dexamethasone (from Sigma, St. Louis, MO) is dissolved in 100% ethanol and diluted
with water (final: 10% ethanol:90% water, vol:vol). Groups treated with vehicle-
vehicle, vehicle-dexamethasone, and Ru486-dexamethasone are included in each
35 screen. The compounds are tested vs. dexamethasone only. Three hours after the
injection of dexamethasone the rats are sacrificed by decapitation. A sample of liver
25 (0.3 g) is excised and placed in 2.7 ml of ice cold buffer and homogenized with a
polytron. To obtain cytosol the liver homogenate is centrifuged at 105,000g for 60
min and the supernatant is stored at -80 °C until analysis. TAT is assayed on 100 ul
40 of a 1:20 dilution of the 105,000g supernatant using the method of Granner and
Tomkins (Methods in Enzymology 17A: 633-637, 1970) and a reaction time of 8-10
30 minutes. TAT activity is expressed as umol product/min/g liver.

45 Interpretation: Treatment data are analyzed by using analysis of variance
(ANOVA) with protected least significant difference (PLSD) post-hoc analysis.
50 Compounds are considered active in this test if the TAT activity in the group

pretreated with compound prior to dexamethasone administration is significantly ($P < 0.05$) decreased relative to the TAT activity in the vehicle-dexamethasone treated group.

The following is a description of an assay for determining the effect of a compound on two typical genes that are upregulated during an inflammatory response. This assay, the glucocorticoid inhibition of IL-1 (Interleukin-1) induced MMP-1 (Matrix Metalloproteinase-1) and IL-8 (Interleukin-8) production in human chondrosarcoma cells, is conducted as follows: SW1353 human chondrosarcoma cells (obtained from ATCC) from passage 12 through passage 19 are used in a 96 well format assay. Cells are plated at confluence into 96 well plates in DMEM (Dulbecco's Modified Eagle Medium) with 10% fetal bovine serum and incubated at 37 °C, 5% CO₂. After 24 hours, serum containing media is removed and replaced with 200 ul/well DMEM containing 1 mg/L insulin, 2 g/L lactalbumin hydrosylate, and 0.5 mg/L ascorbic acid and returned to incubation at 37 °C, 5% CO₂. The following morning, the serum free media is removed and replaced with 150 ul/well fresh serum free media containing +/- 20 ng/ml IL-1 beta, +/- 5 nM dexamethasone, +/- compound. All conditions are completed in triplicate using only the inner 60 wells of the 96 well plate. Outside surrounding wells of plate contain 200 ul of serum free DMEM. Plates are incubated at 37 °C, 5% CO₂. At 24 hours after addition of IL-1, 25 ul of sample from each well is removed under aseptic conditions for IL-8 production analysis. Samples are stored at -20 °C until time of analysis. IL-8 production is assessed using the Quantikine human IL-8 ELISA kit from R&D Systems (D8050) on samples diluted 60-fold in RD5P Calibrator Diluent, following the manufacturer's protocol. The percent of the average IL-1 control is determined for the average of each of the triplicate samples following subtraction of the average signal from untreated cells. IC₅₀'s are determined from log linear plots of the percent of control versus the concentration of inhibitor. At 72 hours after IL-1 addition, the remaining media is removed and stored at -20 °C until time of MMP-1 production analysis. MMP-1 production is assessed via the Bio-Trak MMP-1 ELISA kit from Amersham (RPN2610) on 100 ul of neat sample following the manufacturer's protocol.

The percent of the average IL-1 control is determined for the average of each of the triplicate samples following subtraction of the average signal from untreated cells. IC₅₀'s are determined from log linear plots of the percent of control versus the

concentration of inhibitor. Dexamethasone has proven to be a good positive control inhibitor of both IL-8 and MMP1 expression ($IC_{50}=5nM$).

The following compounds of the present invention are preferred:

- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(4-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];
- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(2-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];
- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(3-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];
- carbamic acid, [2-(dimethylamino)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)];
- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-pyrazinyl-, [4bS-(4b α ,7 α ,8a β)];
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(4-pyridinylmethoxy)-, [2R-(2 α ,4a α ,10a β)];
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-pyridinylmethoxy)-, [2R-(2 α ,4a α ,10a β)];
- 2-phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)];
- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)];
- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4bS-(4b α ,7 α ,8a β)];
- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-(2-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-(3,3,3-trifluoropropyl)-, [2S-(2 α ,4a α ,10a β)];
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(3,3,3-trifluoropropyl)-, [2S-(2 α ,4a α ,10a β)];
- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-, (4bS,7S,8aR);
- 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR);

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-4b-(phenylmethyl)-N-3-pyridinyl-, (4bS,7R,8aR)-;

2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(trifluoromethyl)-, (2R,4aS,10aR)-; and

2-phenanthrenecarboxamide, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(trifluoromethyl)-, (4bS, 7R, 8aR)-.

EXAMPLES

Preparation 1 1-Benzyl-6-methoxy-3,4-dihydro-1H-naphthalen-2-one

A solution of 51 g (0.289 mol) of 6-methoxy-2-tetralone of formula A-1 wherein D is C, R₁₀ is methoxy; R₁₄, R₁₅ and R₁₆ are each H, and 24.2 mL (0.289 mol) of pyrrolidine in 1.5 L of toluene was heated to reflux, over a Dean-Stark trap, overnight. After removal of the azeotroped water, the reaction mixture was cooled to RT, concentrated to an oil, and dissolved in 725 mL of dioxane. To this solution was added 52 mL (0.434 mol) of benzyl bromide and the resulting solution was heated to reflux overnight. Water (100 mL) was added to the solution the resultant mixture was heated to reflux for an additional 2 h. The mixture was cooled to room temperature and poured into a solution of 1 N HCl and extracted 3 times with EtOAc. The organic layers were washed with H₂O and saturated NaHCO₃, then dried over Na₂SO₄, filtered, and evaporated to dryness. The crude product was purified by flash chromatography over SiO₂ using 10% EtOAc to 15% EtOAc in hexanes as the gradient eluant to give 65.2 g of the title product of this preparation as a yellow oil (85%). IR (neat) 2937, 1712, 1500 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.41-2.59 (m, 3H), 2.76 (dt, 1H, J = 5.4, 15.5), 3.15-3.70 (m, 2H), 3.67 (t, 1H, J = 6.3), 3.77 (s, 3H), 6.67-6.70 (m, 2H), 6.81 (d, 1H, J = 8.1), 6.87-6.89 (m, 2H), 7.13-7.17 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 27.44, 38.19, 39.19, 54.13, 55.14, 112.11, 112.96, 126.30, 128.07, 128.26, 129.35, 129.53, 138.05, 138.20, 158.30, 212.41; MS m/z 267 (M+H)⁺.

Preparation 2 1(R)-Benzyl-6-methoxy-1(S)-(3-oxo-butyl)-3,4-dihydro-1H-naphthalen-2-one

A solution of 62 g (0.23 mol) of the title product of Preparation 1 and 28 mL, (0.23 mol) of freshly distilled (S)-(-)-alpha-methyl benzylamine in 100 mL of toluene was heated to reflux, over a Dean-Stark trap, overnight. After removal of the azeotroped water, the imine solution was cooled to 0 °C and 21 mL (0.26 mol) of freshly distilled methylvinylketone was added dropwise to the solution. The solution

5 was stirred at 0 °C for 30 min then heated to 40 °C overnight. The reaction solution
was cooled to 0° C and 17 mL of acetic acid and 14 mL of H₂O were added and the
10 resultant solution was allow to warm to RT for 2 h. The solution was poured into H₂O
and extracted three times with EtOAc. The combined organic layers were washed
5 with 1 N HCl, H₂O, saturated NaHCO₃, then dried over Na₂SO₄, filtered, and
evaporated to dryness. The crude product was purified by chromatography over SiO₂
15 using 15% EtOAc to 35% EtOAc in hexanes as the gradient eluant to give 48 g of the
title product of this preparation as a yellow solid. ¹HNMR (400 MHz, CDCl₃) δ 1.38
(s, 3H), 1.40-1.51 (m, 2H), 1.64 (ddd, 1H, J = 2.1, 4.5, 13), 1.97 (broad s, 1H), 2.20
10 (dt, 1H, J = 4.5, 13), 2.59 (d, 1H, J = 6.6), 3.08 (d, 1H, J = 18), 3.16 (d, 1H, J = 16),
3.33 (dd, 1H, J = 6.6, 18), 3.62 (d, 1H, J = 16), 3.72 (s, 3H), 6.57 (d, 1H, J = 2.5),
20 6.67 (dd, 1H, J = 2.5, 8.8), 7.00-7.23 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 27.90,
32.79, 34.40, 38.43, 41.49, 53.51, 55.12, 58.47, 79.06, 112.05, 113.09, 125.37,
127.63, 127.69, 130.27, 132.21, 135.45, 138.65, 157.88, 213.49; MS *m/z* 337
25 (M+H)⁺, 319 (M-OH)⁺.

Preparation 3 1(*S*)-Benzyl-6-methoxy-1(*R*)-(3-oxo-butyl)-3,4-dihydro-1H-
naphthalen-2-one

30 The title product of this preparation was prepared using a method analogous
to Preparation 2, using (*R*)-(+)-alphamethyl benzylamine in the initial imine formation.
20 Starting with 4.64 g 1-benzyl-6-methoxy-3,4-dihydro-1H-naphthalen-2-one produced
3.58 g of the title product of this preparation as a yellow solid. ¹HNMR (400 MHz,
CDCl₃) δ 1.38 (s, 3H), 1.40-1.51 (m, 2H), 1.64 (ddd, 1H, J = 2.1, 4.5, 13), 1.97
35 (broad s, 1H), 2.20 (dt, 1H, J = 4.5, 13), 2.59 (d, 1H, J = 6.6), 3.08 (d, 1H, J = 18),
3.16 (d, 1H, J = 16), 3.33 (dd, 1H, J = 6.6, 18), 3.62 (d, 1H, J = 16), 3.72 (s, 3H), 6.57
25 (d, 1H, J = 2.5), 6.67 (dd, 1H, J = 2.5, 8.8), 7.00-7.23 (m, 6H); ¹³C NMR (100 MHz,
CDCl₃) δ 27.90, 32.79, 34.40, 38.43, 41.49, 53.51, 55.12, 58.47, 79.06, 112.05,
40 113.09, 125.37, 127.63, 127.69, 130.27, 132.21, 135.45, 138.65, 157.88, 213.49; MS
m/z 337 (M+H)⁺, 319 (M-OH)⁺.

Preparation 4 2(3*H*)-Phenanthrenone, 4a-[(4-isopropylaminophenyl)methyl]-
4,4a,9,10-tetrahydro-7-hydroxy-, (*S*)-

45 30 To a stirring solution of 200 mg of the title product of Preparation 18 in 0.216
mL of AcOH, 3 mL of acetone and 3 mL of dichloroethane under N₂ atmosphere was
added 373 mg of NaBH(OAc)₃ at RT. The reaction mixture was stirred at RT for 2 h,
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then quenched with NaHCO₃ (sat). The mixture was extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness.

Purification by flash chromatography over SiO₂ using 30% EtOAc in hexanes as the eluant afforded 108 mg of the title product of this preparation as white powder (47%).

MS *m/z* 362 (M+H)⁺.

Preparation 5 2(1*H*)-Phenanthrenone, 4a-[[3-(dimethylamino)phenyl]methyl]-3,4,4a,9,10,10a-hexahydro-7-hydroxy-, (4a*S*-*cis*)-

A solution of 255 mg of the title product of Preparation 19 in 0.11 mL of formaldehyde (37% w/w), 255 mg of 5% Pd(OH)₂/C and 10 mL of EtOH was shaken under 50 psi (which is about 3.3 atm.) H₂ pressure for 2 days. The mixture was filtered and concentrated to dryness. Purification by flash chromatography SiO₂ using 2% EtOAc in hexanes to 40% EtOAc in hexanes as the gradient elutant afforded 133 mg (48%) of the title product of this example as white fluffy powder. MS *m/z* 450 (M+H)⁺.

Preparation 6 1-Naphthalenepropanoic acid, 1,2,3,4-tetrahydro-6-methoxy-2-oxo-1-(phenylmethyl)-, methyl ester

To a solution of 3.18 g of the title compound of Preparation 1 in 30 mL of anhydrous MeOH was added 31 mL of 0.5 M NaOMe/MeOH at -15 °C under nitrogen atmosphere. This solution was stirred vigorously while 1.5 mL of fresh distilled methyl acrylate was added dropwise at -15 °C. The mixture was stirred for 1 h at 0 °C and then allowed to settle for 5 min. The precipitate was collected by filtration and the filter cake was washed with MeOH to yield 2 g (52%) of the title product of this preparation as white solid. MS *m/z* 353 (M+H)⁺.

Preparation 7 1-Naphthalenepropanoic acid, 1,2,3,4-tetrahydro-6-methoxy-2-oxo-1-(phenylmethyl)-

A solution of 200 mg of the title product of Preparation 6 and 92 mg of Na₂CO₃ in 8 mL of MeOH and 10 mL of water was heated to reflux for 30 min. The mixture was cooled and adjusted to pH around 5 with 1 N HCl solution. NaCl was added to make a saturated solution. The solution was extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The title product of this preparation was obtained in 98% yield as white solid. MS *m/z* 339 (M+H)⁺.

Preparation 8 3*H*-Naphtho[2,1-*b*]pyran-3-one, 1,2,4a,5,6,10b-hexahydro-8-methoxy-10b-(phenylmethyl)-

To a solution of 199 mg of the title product of Preparation 7 in 5 mL of ethanol was added 67 mg of sodium borohydride at 0 °C under N₂ atmosphere. The mixture was then allowed to stirred overnight at room temperature. The solution was then acidified to pH 1 with 1 N HCl solution and extracted with EtOAc (X3), dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC SiO₂ using 35% EtOAc in hexanes as the elutant afforded 73 mg (37%) of the title product of this preparation as white fluffy powder. MS *m/z* 323 (M+H)⁺.

Preparation 9 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-[4-(*t*-butyldimethylsiloxymethyl)phenyl]-2-propenyl]-, [2*R*-(2α,4α(*E*),10aβ)]-

The title compound of this preparation was prepared by procedures analogous to those described below in Example 35.

Preparation 9a Carbamic acid, dimethyl-, 4b-[2-acetaldehydo]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4*bS*-(4bα,7α,8aβ)]-

To a stirred solution of 4a(2*H*)-phenanthreneacetaldehyde, 2-(1-propynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-, [2*R*-(2α,4α,10aβ)]- (1.5g) in THF were added sequentially 4-dimethylaminopyridine (0.12g), triethylamine (1.8g) and dimethylcarbonyl chloride (1.6g). After 18 h, the heterogeneous mixture was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, the organic layer was dried over sodium sulfate and concentrated in vacuo. The resulting oil was purified by flash chromatography on silica gel (30-50% ethyl acetate/hexanes) to afford the title compound of this preparation as a colorless solid, 2.3g.

Preparation 10 Carbamic acid, dimethyl-, 4b-[2-hydroxyethyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4*bS*-(4bα,7α,8aβ)]-

To a cooled (-78 °C), stirred solution of the title product of Preparation 9a (2.3 g) in tetrahydrofuran (60 mL) was added a 1 M solution of diisobutylaluminum hydride in cyclohexane (8 mL). After 2.5 h, the reaction was quenched with 0.5 M sodium potassium tartrate and the resulting mixture was stirred overnight at room temperature. The two-phase mixture was extracted with ethyl acetate (3x), the combined extracts washed with brine, dried over sodium sulfate and concentrated in

vacuo to afford a colorless foam. Flash chromatography on silica gel (50-75% ethyl acetate/hexanes) afforded the title product of this preparation a colorless foam, 1.9 g.

Preparation 11 8-R,Sa-Benzyl-6-ethoxy-3,7,8,8a-tetrahydro-2H-naphthalen-1-one

5 A solution of 8-R,Sa-benzyl-3,4,8,8a-tetrahydro-2H,7H-naphthalene-1,6-dione (5.0 g), triethylorthoformate (13 mL), p-toluenesulfonic acid (200 mg), ethanol (1.5 mL) in toluene (100 mL) was heated at 80 °C for 1.5 h. The reaction solution was cooled, diluted into ethyl ether, washed with 1N NaOH, water, brine, dried over sodium sulfate and concentrated in vacuo to afford a red oil. Filtration (20% ethyl ether/hexanes) through a pad of Florisil® provided the title product of this preparation as a red solid, 5.7 g.

Preparation 12 (cis/trans)-8-R,Sa-Benzyl-6-ethoxy-3,4,4a,5,8,8a-hexahydro-2H-naphthalen-1-one

15 A solution of the title product of Preparation 11 (2 g) in ethanol (56 mL) was hydrogenated at 1 atm of hydrogen pressure over 2% strontium carbonate (0.2 g) for 4.5 h. After removal of catalyst by filtration and concentration of the filtrate in vacuo, the trans and cis isomers of the title product of this preparation were separated by chromatography on silica gel (0-2% ethyl acetate/hexanes). The cis isomer (0.1 g) eluted first with the trans isomer (1.2 g) predominating.

20 Preparation 13 (trans)-8-R,Sa-Benzyl-2-bromo-6-ethoxy-3,4,4a,5,8,8a-hexahydro-2H-naphthalen-1-one

35 To a cooled (0 °C), stirred solution of lithium diisopropylamide (prepared from diisopropylamine (0.17 mL) and n-butyllithium (0.42 mL, 2.5 M in hexanes)) in tetrahydrofuran (9 mL) was added a solution of (trans)-8-R,Sa-benzyl-6-ethoxy-3,4,4a,5,8,8a-hexahydro-2H-naphthalen-1-one (0.25 g) in tetrahydrofuran (4 mL). After 30 min, the solution was cooled to -78 °C and a solution of n-bromosuccinimide (0.2 g) in tetrahydrofuran (9 mL) was added. After 1 h, the reaction was quenched with saturated aqueous sodium bicarbonate, extracted with ethyl ether, the organic layers were combined, dried over sodium sulfate and concentrated in vacuo. The resulting oil was purified by flash chromatography on silica gel (0-1% ethyl acetate/hexanes) to afford the title compound of this preparation as an oil (200 mg). The cis-isomer of the title product of Preparation 12 can be analogously reacted.

50 Preparation 14 (trans)-8a-Benzyl-2-bromo-hexahydro-naphthalene-1,6-dione

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A solution of the title product of Preparation 13 (0.15 g) in a solution of ethanol (8 mL) containing 2.5% concentrated sulfuric acid and 1% water was stirred for 2 h. The reaction was diluted with ethyl ether, washed with sat. sodium bicarbonate, brine, dried over sodium sulfate and concentrated in vacuo to afford an oil. Flash chromatography on silica gel (15% ethyl acetate/hexanes) afforded the title compound of this preparation as a colorless solid, 53 mg. The cis-isomer can be similarly reacted.

Preparation 15 (trans)-8-R,Sa-Benzyl-6-ethoxy-1-oxo-1,2,3,4,4a,5,8,8a-octahydro-naphthalene-2-carbaldehyde

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To a cooled (0 °C), stirred solution of the trans isomer of the title product of Preparation 12 (2.1 g) and ethyl formate (2.2 g) in tetrahydrofuran (8 mL) was added potassium t-butoxide (15.6 mL, 1 M in THF). The reaction solution was maintained at 0 °C for 0.5 h and at room temperature for 6 h, quenched with sat. aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated in vacuo to afford the title compound of this preparation as a red oil, 2.3 g.

Preparation 16 Phenol, 4-[4-(chloroethynyl)-4-hydroxy-1-(phenylmethyl)cyclohexyl]-

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The title compound of this preparation was prepared by procedures analogous to those described below in Example 8. MS: 342 (M+1)⁺.

Preparation 17 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, (4a*S*-*cis*)

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The title compound of this preparation was prepared by procedures analogous to those described below in Example 7. MS: 323 (M+1)⁺.

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Preparation 18 2(3*H*)-Phenanthrenone, 4a-[(4-aminophenyl)methyl]-4,4a,9,10-tetrahydro-7-hydroxy-, (*S*)-

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The title compound of this preparation was prepared by procedures analogous to those described below in Example 3. MS: 321 (M+1)⁺.

Preparation 19 2(1*H*)-Phenanthrenone, 4a-[(3-aminophenyl)methyl]-3,4,4a,9,10,10a-hexahydro-7-hydroxy-, (4a*S*-*cis*)-

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The title compound of this preparation was prepared by procedures analogous to those described below in Preparation 5. MS: 322 (M+1)⁺.

Preparation 20 Pyridine, 3-[[[(2R,4'aS,10'aR)-3',4',4'a,9',10',10'a-hexahydro-4'a-(phenylmethyl)spiro[oxirane-2,2'(1'H)-phenanthren]-7'-yl]oxy]methyl]-

The title compound of this preparation was prepared by procedures analogous to those described below in Example 76. MS: 413 (M+1)⁺.

Preparation 21 Pyridine, 3-[[[(2R,4'aS,10'aR)-3',4',4'a,9',10'a-hexahydro-4'a-(phenylmethyl)spiro[oxirane-2,2'(1'H)-phenanthren]-7'-yl]oxy]methyl]-2-methyl-

The title compound of this preparation was prepared by procedures analogous to those described below in Example 76. MS: 427 (M+1)⁺.

Preparation 22 Pyridine, 2-[[[(2R, 4'aS, 10'aR)-3',4',4'a,9',10',10'a-hexahydro-4'a-(phenylmethyl)spiro[oxirane-2,2'(1'H)-phenanthren]-7'-yl]oxy]methyl]-

The title compound of this preparation was prepared by procedures analogous to those described below in Example 76. MS: 413 (M+1)⁺.

Example 1 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-methoxy-4a-(phenylmethyl)-, (S)-

A solution of 48 g (143 mmol) of the title product of Preparation 2 and 71 mL of 1 M sodium methoxide in 100 mL of methanol was stirred at room temperature for 15 min, then heated to 75 °C for 3 h. The solution was cooled to 0 °C, 8.2 mL of acetic acid was added dropwise, and the solution was concentrated to an oil. The oil was dissolved in EtOAc, washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered, and evaporated to dryness. The crude product was purified by chromatography over SiO₂ using 15% EtOAc to 35% EtOAc in hexanes as the gradient eluant to give 44 g 2(3*H*)-phenanthrenone, 4,4a,9,10-tetrahydro-7-methoxy-4a-(phenylmethyl)-, (S)- as an off-white powder (60% from 1-benzyl-6-methoxy-3,4-dihydro-1*H*-naphthalen-2-one). Recrystallization from EtOAc/hexane afforded 35 g of the title product of this example as a white crystalline solid. mp 101-102 °C; IR (neat) 1667, 1500 cm⁻¹; ¹H NMR (CDCl₃) 1.83-1.90 (m, 1H), 2.02 (dt, 1H, J = 5.5, 14), 2.27 (dt, 1H, J = 4.3, 14), 2.44-2.51 (m, 2H), 2.64-2.79 (m, 3H), 3.14 (d, 1H, J = 13), 3.21 (d, 1H, J = 13), 3.78 (s 3H), 5.96 (s, 1H), 6.54 (d, 1H, J = 2.6), 6.71 (d, 2H, J = 7.1), 6.77 (dd, 1H, J = 2.6, 8.7), 7.06-7.23 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 30.71, 32.10, 34.62, 36.09, 43.62, 46.36, 55.20, 112.78, 112.84, 125.53, 126.68, 127.96, 128.12, 130.08, 133.01, 137.24, 137.28, 157.75, 169.16, 198.81; MS *m/z* 319

(M+H)⁺. Anal. Calcd. for C₂₂H₂₂O₂: C, 82.99; H, 6.96; N, 0. Found: C, 83.21; H, 7.08; N, <0.10.

Example 2 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-methoxy-4a-(phenylmethyl)-, (*R*)-

The title product of this preparation was prepared using a method analogous to Example 1. Starting with 3.53 g of the title product of Preparation 3 produced 2.78 g of the title product of this example as an off-white powder (51% from 1-benzyl-6-methoxy-3,4-dihydro-1*H*-naphthalen-2-one. Recrystallization from EtOAc/hexane afforded 2.15 g of the title product of this example as a white crystalline solid. All physical constants are the same as reported for the title product of Example 1. Anal. Calcd. for C₂₂H₂₂O₂: C, 82.99; H, 6.96; N, 0. Found: C, 83.17; H, 7.13; N, <0.10.

Example 3 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-hydroxy-4a-(phenylmethyl)-, (*S*)-

To a stirring solution of 40 g (0.126 mol) of the title product of Example 1 (which was made by procedures described in Example 1) and 46.5 g (0.126 mol) of tetrabutylammonium iodide in 630 mL of dichloromethane at -78 °C under N₂ atmosphere was added 300 mL of 1 M boron trichloride in methylene chloride. The resultant solution was allowed to warm to RT for 1.5 h, then poured into excess ice and stirred rapidly, overnight. The mixture was extracted with dichloromethane, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 20%EtOAc to 60%EtOAc in hexanes as the gradient eluant afforded 33.3 g of the title product of this example as an off-white powder (87%). ¹H NMR (400 MHz, CD₃OD) δ 1.81-2.00 (m, 2H), 2.26 (dt, 1H, J = 4.2, 13), 2.40 (dd, 1H, J = 4.5, 18), 2.53 (ddd, 1H, J = 1.7, 5.6, 14), 2.58-2.80 (m, 3H), 3.20 (d, 1H, J=13), 3.26 (d, 1H, J = 13), 5.92 (s, 1H), 6.45 (d, 1H, J = 2.5), 6.67 (dd, 1H, J = 2.5, 8.5), 6.76 (d, 2H, J = 6.6), 7.05-7.14 (m, 4H); ¹³C NMR (100 MHz, CD₃OD) δ 30.22, 32.03, 34.08, 36.04, 43.73, 45.97, 113.76, 113.91, 124.50, 126.25, 127.49, 127.94, 129.84, 131.86, 137.0, 137.71, 155.34, 171.73, 200.33; MS *m/z* 305 (M+H)⁺.

Example 4 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-hydroxy-4a-(phenylmethyl)-, (*R*)-

The title product of this example was prepared using a method analogous to Example 3. Starting with 1.8 g of the title product of Example 2 produced 1.3 g of the

5 title product of this example as a white solid (75%). All physical constants are the same as reported for the title product of Example 3.

10 Example 5 2,7-Phenanthrenediol, 2,3,4,4a,9,10-hexahydro-4a-(phenylmethyl)-2-(1-propynyl)-, (2*R*-*cis*)- and 2,7-
5 Phenanthrenediol, 2,3,4,4a,9,10-hexahydro-4a-(phenylmethyl)-2-(1-propynyl)-, (2*S*-*trans*)-

15 To a stirring solution of 5 mL of THF saturated with propyne gas at 0 °C was added 4 mL of 0.5 M lithium diisopropylamide in THF and the resultant mixture stirred under nitrogen atmosphere for 20 min. A solution of 50 mg (0.16 mmol) of the title
10 product of Example 3 in 2 mL of THF was added dropwise, and the reaction mixture was warmed to RT and stirred for 16 h. Saturated, aqueous ammonium chloride was added, and the mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 2%
20 acetone in dichloromethane to 4% acetone in dichloromethane with 0.5% triethylamine as the gradient eluant afforded 25 mg (45%) of the first listed title product of this example (higher R_f) and 5 mg (9%) of the second listed title product of
25 this example.

30 The physical properties of the first listed title product of this example are as follows: ¹H NMR (400 MHz, d₆acetone) δ 1.67 (s, 3H), 1.67-1.80 (m, 2H), 2.00-2.22 (m, 2H + d₆acetone), 2.26 (ddd, 1H, J = 2.9, 4.2, 7.0), 2.60-2.78 (m, 3H),
20 3.01, (d, 1H, J = 13), 3.05 (d, 1H, J = 13), 4.30 (s, 1H), 5.52 (s, 1H), 6.49, (d, 1H, J = 2.6), 6.55 (dd, 1H, J = 2.6, 8.5), 6.67 (d, 1H, J = 8.5), 6.76-6.80 (m, 2H),
35 7.08-7.13 (m, 3H), 8.06, (s, 1H); ¹³C NMR (100 MHz, d₆acetone) δ 2.5, 31.4, 33.3, 35.6, 41.8, 46.8, 54.8, 65.8, 77.8, 83.9, 113.1, 114.4, 126.0, 127.4, 127.7,
25 128.4, 130.6, 134.0, 137.2, 138.7, 141.1, 155.1; MS *m/z* 327 (M-OH)⁺.

40 The physical properties of the second listed title product of this example are as follows: ¹H NMR (400 MHz, d₆acetone) δ 1.77 (s, 3H), 1.77-2.30 (m, 5H + d₆acetone), 2.58-2.78 (m, 3H), 2.96, (d, 1H, J = 13), 3.02 (d, 1H, J = 13), 4.06 (s
45 1H), 5.60 (s, 1H), 6.47 (d, 1H, J = 2.3), 6.56 (dd, 1H, J = 2.3, 8.3), 6.78-6.82 (m, 3H), 7.10-7.14 (m, 3H), 8.03 (s, 1H); ¹³C NMR (100 MHz, d₆acetone) δ 2.5, 30.9, 31.6, 35.3, 41.9, 46.3, 54.6, 63.1, 76.8, 84.7, 113.1, 114.3, 126.0, 126.7, 127.4,
30 128.4, 130.5, 134.0, 137.3, 138.7, 142.3, 155.1; MS *m/z* 327 (M-OH)⁺.

Example 6 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a- (phenylmethyl)-, (4a*S-trans*)-

Ammonia (1.5 L) was condensed into a round bottom flask at -78 °C equipped with a dry ice reflux condenser at -78 °C and a mechanical stirrer. To this flask was added 0.7 g (99 mmol) of lithium wire and the solution turned dark blue. A solution of 10 g (32.8 mmol) of the title product of Example 3 in 400 mL of 1:1 dioxane:ether was added to the mixture slowly in order to keep the reaction a dark blue. As the blue color dissipated, a small amount of lithium wire was added to the mixture to regenerate the blue color. The total amount of lithium added to the reaction mixture did not exceed 3.5 g (495 mmol). After the complete addition of 10 g of the title product of Example 3, the reaction was stirred an additional 30 min, then 14 g of solid ammonium chloride was added and immediate dissipation of the blue color was observed. H₂O was added to the mixture and it was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. The crude product was purified by flash chromatography over SiO₂ using 15% EtOAc to 20% EtOAc in hexanes as the gradient eluant to afford 8.16 g of the title product of this example as a white solid (81%). ¹H NMR (400 MHz, CD₃OD) δ 1.52 (dt, 1H, J = 4.5, 13), 1.64-1.71 (m, 1H), 1.90-2.15 (m, 2H), 2.27 (ddd, 1H, J = 2.5, 3.7, 15), 2.39 (dm, 1H, J = 15), 2.48 (ddd, 1H, J = 2.0, 6.5, 13), 2.72 (t, 1H, J = 14), 2.84 (d, 1H, J = 13), 2.89-3.01 (m, 3H), 3.22 (d, 1H, J = 13), 6.17 (d, 1H, J = 8.5), 6.24 (dd, 1H, J = 2.5, 8.5), 6.53 (d, 1H, J = 2.5), 6.65-6.68 (m, 1H), 7.04-7.13, (m, 3H); ¹³C NMR (100 MHz, CD₃OD) δ: 27.9, 33.7, 34.8, 36.0, 37.6, 39.4, 43.6, 44.0, 111.3, 114.6, 125.7, 127.0, 127.9, 130.5, 133.4, 136.8, 138.0, 155.1, 212.7; MS *m/z* 307 (M+H)⁺.

Example 7 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a- (phenylmethyl)-, (4a*S-cis*)-

To a solution of 1 g (3.6 mmol) of the title product of Example 3 in 75 mL of ethanol and 0.27 mL of 2M KOH was added 0.15 g of 10% Pd/C. The reaction mixture was shaken under 45 p.s.i. (which is about 3 atm) of H₂ gas for 4 h. Acetic acid (0.035 mL) was added then the mixture was filtered through Celite®, washing the Celite® with ethanol, and then the ethanol was removed under reduced pressure. The resultant residue was partitioned between EtOAc and sat. NaHCO₃, extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. The crude product was purified by flash chromatography over SiO₂ using 25% EtOAc in

5 hexanes as the eluant to afford 947 mg of the title product of this example as a white
solid (86%). ¹H NMR (400 MHz, CD₃OD) δ 1.52-1.60 (m, 1H), 1.87 (ddd, 1H, J = 4.8,
10 11, 14), 2.00-2.35 (m, 6H), 2.39 (dt, 1H, J = 5.2, 14), 2.69-2.92 (m, 2H), 2.96 (d, 1H,
J = 13), 3.00 (d, 1H, J = 13), 6.56-6.58 (m, 2H), 6.88-6.92 (m, 3H), 7.13-7.15, (m,
5 3H); ¹³C NMR (100 MHz, CD₃OD) δ 23.7, 25.3, 34.7, 37.2, 39.6, 40.3, 42.8, 47.7,
113.1, 115.1, 127.3, 128.0, 130.5, 137.2, 137.8, 155.2, 213.9; MS *m/z* 307 (M+H)⁺.

15 Example 8 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-
octahydro-4a-(phenylmethyl)-, [2*R*-(2α,4α,10αβ)]- and 2,7-
Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-
10 octahydro-4a-(phenylmethyl)-, [2*S*-(2α,4αβ,10αα)]-

20 To a stirring solution of 95 mg of cis-dichloroethylene (0.98 mM) in 5 mL of
THF at 0 °C was added 2.5 mL of 0.5 M lithium diisopropylamide in THF and the
resultant mixture was allowed to warm to RT for 30 min under nitrogen atmosphere.

25 A solution of 30 mg (0.098 mmol) of the title product of Example 6 in 0.65 mL of THF
15 was added dropwise, and the reaction mixture was stirred an additional 2 h.
Saturated, aqueous ammonium chloride was added, and the mixture was extracted
with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Initial
30 purification by flash chromatography over SiO₂ using 20% EtOAc in hexanes as the
eluant afforded 30 mg of a light brown solid. Further purification by flash
20 chromatography over SiO₂ using 2% acetone in dichloromethane to 4% acetone in
dichloromethane as a gradient eluant afforded 20 mg (56%) of the first listed title
product of this example (higher R_f) and 7.0 mg (19%) of the second listed title
35 product of this example (lower R_f) as white solids. The physical characteristics of the
first listed title product of this example are as follows: mp 230-232 °C (decomp.); ¹H
25 NMR (300 MHz, CD₃OD) δ 1.40 (mt, 1H, J = 14), 1.64-1.70 (m, 1H), 1.80-2.13 (m,
7H), 2.59 (d, 1H, J = 13), 2.93-2.97 (m, 3H), 6.13 (d, 1H, J = 8.5), 6.25 (dd, 1H, J =
40 2.6, 8.5), 6.54-6.57 (m, 3H), 7.00-7.07 (m, 3H); ¹³C NMR (75 MHz, CD₃OD) δ 25.5,
28.7, 31.8, 37.2, 40.52, 41.71, 43.43, 63.1, 70.7, 74.1, 112.4, 116.1, 126.8, 128.3,
138.9, 132.1, 136.2, 138.3, 139.5, 156.3; MS *m/z* 366 (M+H)⁺, 349 (M-OH)⁺.

45 30 The physical characteristics of the second listed title product of this example
are as follows: mp 216-219 °C (decomp.) ¹H NMR (400 MHz, CD₃OD) δ 1.47 (mt,
1H, J = 14), 1.56-1.62 (m, 1H), 1.80-2.00 (m, 5H), 2.08 (mt, 1H, J = 13), 2.23 (dt, 1H,
50 J = 3.8, 14), 2.59 (d, 1H, J = 13), 2.82-2.93 (m) and 2.95 (d, 1H, J = 13), 6.08 (d, 1H,

J = 8.6), 6.20 (dd, 1H, J = 2.2, 8.6), 6.50 (d, 1H, J = 2.2), 6.54-6.56 (m, 2H), 7.03-7.06 (m, 3H); ¹³C NMR (75 MHz, CD₃OD) δ 25.4, 28.8, 28.9, 36.0, 36.7, 40.4, 42.5, 65.1, 67.3, 75.9, 112.3, 116.1, 126.8, 128.2, 128.8, 132.2, 136.3, 138.3, 139.7, 156.2; MS *m/z* 366 (M+H)⁺, 349 (M-OH)⁺.

- 5 Example 9 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2α,4α,10αβ)]- and 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*S*-(2α,4αβ,10αα)]-

To a stirring solution of 183 mL of THF saturated with propyne gas at 0 °C was added 143 mL of 1 M lithium diisopropylamide in THF and the resultant mixture was stirred under nitrogen atmosphere for 20 min. A solution of 7.3 g (23.8 mmol) of the title product of Example 6 in 250 mL of THF was added dropwise, and the reaction mixture was warmed to RT and stirred overnight. Saturated, aqueous ammonium chloride was added, and the mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 2% acetone in dichloromethane to 4% acetone as the eluant afforded 4.0 g (49 %) of the first listed title product of this example (higher R_f) and 2.4 g (29 %) of the second listed title product of this example as white solids.

Physical characteristics of the first listed title product of this example are as follows: mp 227-229 °C (decomp.); ¹H NMR (400 MHz, CD₃OD) δ 1.42 (mt, 1H, J = 14), 1.61 (ddd, 1H, J = 3.4, 4.1, 8.8), 1.72 (s, 3H), 1.73-1.82 (m, 2H), 1.84-2.10 (m, 5H), 2.55 (d, 1H, J = 13), 2.83-2.93 (m) and 2.94 (d, 3H, J = 13), 6.10 (d, 1H, J = 8.3), 6.23 (dd, 1H, J = 2.5, 8.4), 6.52-6.55 (m, 3H), 7.00-7.05 (m, 3H); ¹³C NMR (62 MHz, CD₃OD) δ 2.5, 24.1, 27.3, 30.5, 35.8, 36.1, 39.1, 40.2, 42.4, 68.9, 79.5, 82.3, 110.9, 114.7, 125.4, 126.8, 127.5, 130.7, 135.1, 136.9, 138.3, 154.8; MS *m/z* 346 (M+H)⁺, 329 (M-OH)⁺.

Physical characteristics of the second listed title product of this example are as follows: mp 222-223 °C (decomp.); ¹H NMR (400 MHz, CD₃OD) δ 1.46 (mt, 1H, J = 14), 1.54-1.60 (m, 1H), 1.83 (s) overlap with 1.75-1.94 (m, 8H), 2.08 (mt, 1H, J = 13), 2.20 (dt, 1H, J = 4, 14), 2.57 (d, 1H, J = 13), 2.88 (t, 2H, J = 8.7), 2.94 (d, 1H, J = 13), 6.08 (d, 1H, J = 8.3), 6.20 (dd, 1H, J = 2.4, 8.3), 6.50 (d, 1H, J = 2.4), 6.53-6.56 (m, 2H), 7.01-7.06 (m, 3H); ¹³C NMR (62 MHz, CD₃OD) δ 1.7, 24.1, 27.4, 27.6, 35.0,

35.2, 36.4, 39.0, 41.6, 65.5, 76.9, 84.5, 110.8, 114.6, 125.3, 126.8, 127.4, 130.7, 135.0, 136.9, 138.4, 154.7; MS m/z 346 (M+H)⁺, 329 (M-OH)⁺.

Example 10 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-[2*R*-(2 α ,4 α ,10 α β)]-

5 A mixture of 975 mg of the first listed title product of Example 9, 195 mg of 10 % Pd/C, and 100 mg K₂CO₃ in MeOH was shaken under 40 p.s.i. (which is about 2.6 atm) of H₂ gas for 16 h. The mixture was filtered through Celite® and concentrated to afford 945 mg of the title product of this example as a white solid. MS: 368 (M+18)⁺.

10 Example 11 Pentanal, 5-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-

20 To a stirring solution of 157 mg of the title compound of Example 314, below, in 4.8 mL of dioxane and 1.2 mL of H₂O was added 72 mg of 4-methylmorpholine-N-oxide, 0.003 mL of pyridine, and 0.18 mL of 2.5 wt. % OsO₄ in *t*-butanol and the reaction mixture was stirred for 4 h. To this mixture was added 776 mg of NaIO₄ and the resultant mixture was stirred overnight. The reaction mixture was poured into H₂O and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 25 % EtOAc in hexanes to 10 % EtOAc in hexanes as the gradient eluant afforded 141 mg of the title product of this example as colorless oil. MS: 417 (M-17)⁺.

30 Example 12 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[[5-(4-morpholinyl)pentyl]oxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-

25 To a stirring solution of 34.6 mg of the title product of Example 11 in 1 mL of AcOH was added 0.014 mL of morpholine and 109 mg of Na₂SO₄ and the resultant mixture was stirred for 15 min. To this mixture was added 24 mg of NaHB(OAc)₃ and the resultant mixture was stirred for 1.5 h. The mixture was cooled to 0 °C and sat. Na₂CO₃ added until the pH of the mixture was approximately 8 to 9. The reaction mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5 % MeOH in dichloromethane to MeOH as the eluant afforded 26.6 mg of the title product of this example as a white solid. MS: 506 (M+1)⁺.

Example 13 Methanesulfonic acid, trifluoro, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α , 7 α , 8a β)]-

To a stirring solution of 4.14 g of the first listed title compound of Example 9 (which was prepared by procedures described in Example 9), 1.95 mL of 2,6-lutidine, and 292 mg of 4-dimethylaminopyridine in 150 mL of dichloromethane at -40 °C under nitrogen was added 2.6 mL of trifluoromethylsulfonic anhydride. The resultant mixture was stirred for 0.5 h at -40 °C, 0.5 h at 0 °C, then 1.5 h at RT. The reaction mixture was poured into 1 N HCL and extracted with dichloromethane. The organic layer was washed with water, sat. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 15% EtOAc in hexanes to 20% EtOAc in hexane as the gradient eluant afforded 4.4 g (77%) of the title product of this example as a white solid. ¹H NMR (400 MHz, C₆D₆) δ 6.07 (d, 1H, J = 8.4), 6.63 (d, 1H, J = 2.5).

Example 14 2-Phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, methyl ester, [4bS-(4b α ,7 α ,8a β)]-

A mixture of 1.18 g of the title product of Example 13, 0.27 g of 1,3-bis(diphenylphosphino)-propanol, 2.54 mL of triethylamine, and 0.1 g of palladium acetate in 40 mL of 1:1 DMF / MeOH was shaken under 60 p.s.i. (which is about 4 atm) carbon monoxide at 70 °C for 4 h. The reaction mixture was concentrated to remove MeOH. The mixture was poured into 1:1 hexane / EtOAc, washed with 50 % brine, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 23 % EtOAc in hexanes to 28 % EtOAc in hexane as the gradient eluant afforded 0.79 g (82 %) of the title product of this example as a white solid. MS: 371 (M-17)⁺.

Example 15 2-Phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-

A stirring mixture of 1.0 g of the title product of Example 13, 0.4 g of tetrakis(triphenylphosphine)palladium(0), and 0.17 g of zinc(II)cyanide in 9.5 mL of 1-methyl-2-pyrrolidinone (NMP) under nitrogen was heated to 90 °C for 4 h. The reaction mixture was poured into sat. NaHCO₃, filtered through Celite®, and

5 extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and
concentrated to dryness. Purification by flash chromatography over SiO₂ using 20%
10 EtOAc in hexanes to 30 % EtOAc in hexanes as the gradient eluant afforded 0.64 g
(86 %) of the title product of this example as a white solid. MS: 338 (M-17)*.

5 Example 16 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
(phenylmethyl)-2-(1-propynyl)-7-(2-pyridinyl)-, [2*R*-
15 (2α,4α,10aβ)]-

Nitrogen gas was bubbled through a solution 300 mg of the title product of
Example 13, 70 mg of 1,1'-bis(diphenylphosphino)ferrocene, and 28 mg of palladium
10 acetate in THF for 5 min. Under nitrogen atmosphere, the solution was cooled to -78
°C and 3.78 mL of 0.5 M bromo-2-pyridyl zinc in THF was added. The solution was
warmed to RT then heated to 70 °C overnight. After cooling to RT, sat. NH₄Cl was
20 added and the resultant mixture was extracted with EtOAc, dried over Na₂SO₄,
filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂
25 using 20% EtOAc in hexanes as the eluant afforded 173 mg (67 %) of the title
product of this example as a white solid. MS: 408 (M+1)*.

Example 17 2-Phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-
7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4*bS*-
30 (4bα,7α,8aβ)]-

20 To a stirring solution of 170 mg of the title product of Example 14 in 4 mL of
THF was added 0.26 mL of 2 N KOH and the resultant solution was heated to reflux
for 3 days. An additional 0.75 mL of 2 N KOH was added and the mixture was
35 heated to reflux overnight. The reaction mixture was cooled to RT, diluted with a
small amount of water, and washed with diethyl ether. The aqueous layer was
25 acidified with 2N HCl and extracted with EtOAc. The organic layer was dried over
Na₂SO₄, filtered, and concentrated to dryness to yield 155 mg of the title product of
40 this example as an off-white solid. MS: 357 (M-17)*.

Example 18 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-*N*-[3-(1*H*-imidazol-1-yl)propyl]-4b-(phenylmethyl)-7-(1-
45 propynyl)-, [4*bS*-(4bα,7α,8aβ)]-

30 To a stirring solution of 1-(3-aminopropyl)imidazole in 1 mL of
dichloromethane at 0 °C under N₂ was added 0.1 mL of 2.0 M trimethylaluminum in
hexane. The mixture was stirred at 0 °C for 20 min. then at RT for 1 h. To this
50

5 mixture was added 20 mg of the title compound of Example 14 in 1 mL of
dichloromethane. The mixture was heated to reflux for 6 h then removed from the
10 heat and stirred at RT for 3 days. To the reaction mixture was added 1 N HCl
dropwise until the aqueous layer was approximately pH 4. The resultant mixture was
5 extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness.
Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane
15 to 10% MeOH in dichloromethane as the gradient eluant afforded 22 mg (88 %) of
the title product of this example as a white solid. MS: 483 (M+1)⁺.

Example 19 2-Phenanthrenemethanol, 4b,5,6,7,8,8a,9,10-octahydro-7-
10 hydroxy- α,α -dimethyl-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-
(4b α ,7 α ,8a β)]-

20 To a stirring solution of 100 mg of the title compound of Example 14 in 2 mL
of THF at 0 °C under N₂ was added 0.77 mL of 1 M methyl magnesium bromide in
butyl ether. The mixture was stirred at 0 °C for 2 h, warmed to RT and stirred an
25 additional 1 h. To the reaction mixture was added 1.2 mL of 1 M methyl magnesium
bromide in butyl ether and the resultant mixture was stirred at RT for 1 h. Sat. NH₄Cl
15 was added and the resultant mixture was extracted with EtOAc, dried over Na₂SO₄,
filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂
30 using 20% EtOAc in hexanes to 30 % EtOAc in hexanes as the gradient eluant
afforded 80.5 mg of the title product of this example as a white solid. MS: 371 (M-
20 17)⁺.

Example 20 2-Phenanthrenemethanol, 4b,5,6,7,8,8a,9,10-octahydro-7-
35 hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-
(4b α ,7 α ,8a β)]-

25 To a stirring solution of 50 mg of the title compound of Example 14 in 2 mL of
dichloromethane at -78 °C under N₂ was added 0.39 mL of 1 M diisobutylaluminum
40 hydride in hexane and the resultant mixture was stirred for 35 min. Methanol (10
drops) was added dropwise to the reaction mixture followed by 2 mL of sat.
Rochelle's salt. The mixture was extracted with dichloromethane. The organic layer
45 was washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated to
dryness. The resultant solid was washed with a small amount of EtOAc to afford 18
mg of the title product of this example as a white solid. MS: 343 (M-17)⁺.

Example 21 2-Phenanthrenemethanol, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, α -methanesulfonate, [4b*S*-(4b α ,7 α ,8a β)]-

To a stirring solution of 20 mg of the title product of Example 20 (which was prepared by procedures described in Example 20) in 0.5 mL of THF at 0 °C under N₂ was added 0.017 mL of methanesulfonyl chloride and 0.02 mL of diisopropylethylamine. After 3 h, the reaction mixture was diluted with EtOAc, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated to give 18 mg of the title product of this example as a yellow solid. ¹H NMR (400 MHz, C₆D₆) δ 4.79 (s, 2H).

Example 22 2-Phenanthrenol, 7-(azidomethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

The title product of Example 21 (18 mg) and 20 mg of sodium azide in 0.5 mL of DMF were heated to 100 °C under N₂ for 3 h. The reaction mixture was cooled to RT, diluted with EtOAc, washed with H₂O and brine, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 20% EtOAc in hexanes as the eluant afforded 18 mg of the title product of this example as a white solid. IR (neat) 2098 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ 4.24 (s, 2H).

Example 23 2-Phenanthrenol, 7-(aminomethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

To a stirring solution of 18 mg of the title product of Example 22 in 1 mL of 2 : 1 : 1 THF : MeOH : H₂O was added 25 mg of triphenylphosphine and the resultant mixture stirred at RT for 1.5 h. The reaction mixture was concentrated to a white residue. To this residue was added diethyl ether and the resultant mixture was extracted with 1 N HCl. The aqueous layer was taken to pH greater than 10 by the addition of 15% NaOH, extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane to 50 % MeOH in dichloromethane with 1 % triethylamine as the gradient eluant afforded 10 mg of the title product of this example as a white solid. MS: 360 (M+1)⁺.

Example 24 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(1H-tetrazol-5-yl)-, [2*R*-(2α,4α,10αβ)]-

To a stirring solution of 42 mg of the title compound of Example 15 in 1 mL of toluene under N₂ was added 4.7 g of dibutyltin oxide and 0.032 mL of trimethylsilylazide. The resultant mixture was stirred at 90 °C for 7 days then at RT for 7 additional days. The reaction mixture was concentrated *in vacuo*, dissolved in MeOH, and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with sat. NaHCO₃, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 10% MeOH in dichloromethane as the eluant afforded 4 mg of the title product of this example as a white solid. MS: 399 (M+1)⁺.

Example 25 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-methoxy-*N*-methyl-4b-(phenylmethyl)-7-(1-propynyl)-, [4*bS*-(4bα,7α,8aβ)]-

To a stirring solution of 168 mg of the title compound of Example 17 (which was prepared by procedures described in Example 17) dichloromethane was added sequentially 53 mg of *N*,*O*-dimethylhydroxylamine hydrochloride, 172 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 121 mg of hydroxybenzotriazole hydrate, and 110 mg of 4-dimethylaminopyridine at RT under N₂. The resultant mixture was stirred at RT overnight, poured into 2 N HCl, and extracted with EtOAc. The organic layer was washed sequentially with 2 N HCl, H₂O, and sat. NaHCO₃, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 3% MeOH in dichloromethane as the eluant afforded 134 mg (71%) of the title product of this example as a colorless oil. MS: 418 (M+1)⁺.

Example 26 1-Propanone, 1-{4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl}-, [4*bS*-(4bα,7α,8aβ)]-

To a stirring solution of 119 mg of the title product of Example 25 in 1.5 mL of THF at -78 °C under N₂ was added 0.86 mL of 1 M ethyl magnesium bromide in THF. The reaction mixture was stirred at -78 °C for 1 h, 0 °C for 2 h, then RT for 2 h. The reaction mixture was poured into 5% HCl in EtOH and stirred for 5 min. The resultant

5 mixture was poured into brine, and extracted with EtOAc. The organic layer was dried
over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash
10 chromatography over SiO₂ using 15% EtOAc in hexanes to 20% EtOAc in hexane as
the gradient eluant afforded 49.5 mg (48%) the title product of this example as a
5 white solid. MS: 387 (M+1)*.

Example 27 2-Phenanthrenemethanol, α -ethyl-4b,5,6,7,8,8a,9,10-
15 octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-
(4b α ,7 α ,8a β)]-

To a stirring solution of 32.3 mg of the title product of Example 26 in 0.8 mL of
10 MeOH was added 3.2 mg of NaBH₄ and the resultant mixture stirred at RT for 2 days.
An additional 2 mg of NaBH₄ was added and the reaction mixture was heated to
20 reflux for 2 h. After cooling to RT, H₂O was added and the mixture concentrated *in vacuo* to remove MeOH. The resultant mixture was extracted with EtOAc, dried over
Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography
25 over SiO₂ using 15% EtOAc in hexanes as the eluant afforded 24 mg of the title
product of this example as a colorless oil. MS: 371 (M-17)*.

Example 28 Carbamic acid, [4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-
30 (phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]-, 1,1-
dimethylethyl ester, [4bS-(4b α ,7 α ,8a β)]-

20 A solution of 124 mg of the title compound of Example 17, 91 mg of
diphenylphosphoryl azide, and 0.046 mL of triethylamine in 1 mL of *t*-butanol was
heated to reflux for 16 h. The solution was concentrated *in vacuo* and the resultant
35 residue was dissolved in EtOAc. The EtOAc solution was washed with 5% citric acid,
H₂O, sat. NaHCO₃, and brine, dried over Na₂SO₄, filtered, and concentrated to
25 dryness. Purification by flash chromatography over SiO₂ using 30% EtOAc in
hexanes to 50% EtOAc in hexanes as the gradient eluant afforded 34.1 mg of the title
40 product of this example as a white solid. MS: 328 (M-17)*.

Example 29 2-Phenanthrenol, 7-amino-1,2,3,4,4a,9,10,10a-octahydro-4a-
45 (phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10a β)]-

30 To a stirring solution of 20 mg of the title product of Example 28 in 0.5 mL of
dichloromethane was added 0.07 mL of trifluoroacetic acid. The solution was stirred
at RT for approximately 1.5 h. Sat. NaHCO₃ was added to the solution. The
resultant mixture was extracted with EtOAc, washed with brine, dried over Na₂SO₄,
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5 filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 20% EtOAc in hexanes as the eluant afforded 7.5 mg of the title product of this example as a white solid. MS: 328 (M+1)⁺.

10 Example 30 2-Phenanthrenecarboxamide, 4b-(2,3-dihydroxypropyl)-
5 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-

15 To a stirring suspension of 303 mg of 2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(2-propenyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]- in 13.5 mL of dioxane and 3.3 mL of H₂O was added 186 mg of 4-methylmorpholine-N-oxide, 0.008 mL of pyridine, and 0.47 mL of 2.5 wt. % OsO₄ in *t*-butanol and the mixture was stirred at RT overnight. To this mixture was added 1:1 sat. NaHCO₃ and sat. NaHSO₃. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to afford 292 mg of the title product of this example as a white solid. MS: 358 (M+1)⁺.

20 Example 31 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-[(2-oxo-1,3-dioxolan-4-yl)methyl]-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-

25 To a stirring solution of 90 mg the title product of Example 30 in dichloromethane at 0 °C under N₂ was added 45 mg of carbonyldiimidazole. The reaction mixture was warmed to RT and stirred for 3 h. The mixture was concentrated to dryness and purified by flash chromatography over SiO₂ using 3 % MeOH in dichloromethane to 5% MeOH in dichloromethane as the gradient eluant to afford 46 mg of the title product of this example as a white solid. MS: 384 (M+1)⁺.

30 Example 32 4a(2H)-Phenanthreneacetaldehyde, 2-(chloroethynyl)-
25 1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-, [2R-(2 α ,4 α ,10a β)]-

35 To a stirring solution of 1.77 g of the title compound of Example 172, below, in 100 mL of dioxane and 25 mL of H₂O was added 1.11 g of 4-methylmorpholine-N-oxide, 0.045 mL pyridine, and 2.8 mL of 2.5 wt. % OsO₄ in *t*-butanol and the reaction mixture stirred for 6 h. To this mixture was added 12 g of NaIO₄ and the resultant mixture stirred overnight. The reaction mixture was poured into H₂O and extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 30%
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EtOAc in hexanes as the eluant afforded 1.04 g of the title product of this example as a white solid. ¹H NMR (400 MHz, D₆-acetone) δ 4.8 (s, 2H).

Example 33 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[2-(1-piperidinyl)ethyl]-, [2*R*-(2α,4α,10aβ)]-

To a stirring solution of 100 mg of the title product of Example 32 in 1.5 mL of AcOH was added 0.062 mL of piperidine and 446 mg of Na₂SO₄ and the resultant mixture was stirred for 15 min. To this mixture was added 100 mg of NaHB(OAc)₃ in two portions and the resultant mixture was stirred for 1.5 h. The mixture was cooled to 0 °C and sat. Na₂CO₃ added until the pH of the mixture was approximately 8 to 9. The reaction mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane to MeOH as the gradient eluant afforded 95 mg of the title product of this example as a white solid. MS: 388 (M+1)⁺.

Example 34 4a(2*H*)-Phenanthreneacetaldehyde, 2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-, oxime, [2*R*-[2α,4α,10aβ]]-

To a stirring solution of 150 mg of the title product of Example 32 in 6 mL of MeOH was added 147 mg of KHCO₃ and 141 mg of hydroxylamine hydrochloride. The reaction mixture was heated to reflux for 3 h then cooled to RT and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane to 8% MeOH in dichloromethane as the gradient eluant afforded 64 mg of the title product of this example as a white solid. MS: 316 (M-17)⁺.

Example 35 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(3-phenyl-2-propenyl)-, [2*R*-(2α,4α(*E*),10aβ)]-

To a stirring solution of 410 mg of diethyl benzylphosphonate in 5 mL of THF at -78 °C under N₂ was added 0.65 mL of 2.5 M butyl lithium in hexane. The reaction mixture was warmed to 0 °C and stirred for 1 h. To the reaction mixture was added 104 mg of the title product of Example 32 in 2 mL of THF and the mixture was stirred an additional 3.5 h. The reaction mixture was poured into sat. NH₄Cl, extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 10 % EtOAc in hexanes to 20% EtOAc in hexane as the gradient eluant afforded 60 mg of the title product of this example as a white solid. MS: 375 (M-17)⁺.

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Example 36 2-Butenoic acid, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-, [2*R*-[2 α ,4 α (*E*),10 α β]]-

To a stirring solution of 2.2 g of the title compound of Example 183, below, in 40 mL of THF was added 11 mL of 2 N KOH and the resultant solution was heated to reflux for 4 h. The reaction mixture was cooled to RT, diluted with a small amount of water, and washed with diethyl ether. The aqueous layer was acidified with 2N HCl and extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness to yield 1.55 g of the title product of this example as an off-white solid. ¹H NMR (400 MHz, CD₃OD) δ 5.66 (d, 1H, J = 15), 6.67-6.80 (m, 1H).

Example 37 Pyrrolidine, 1-[4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-oxo-2-butenyl]-, [2*R*-[2 α ,4 α (*E*),10 α β]]- (Formula F-12: R₂ is OH, R₃ is chloroethynyl, R₅ is H, R₈ is H, R₉ is H, R₁₀ is OH, R₇, R₁₄, R₁₅, R₁₈ are each H, m is 2, R₁₂ and R₁₃ taken together with N are pyrrolidiny) Refer to Scheme F.

To a stirring solution of 168 mg of the title product of Example 36 in dichloromethane was added sequentially 0.67 mL of pyrrolidine, 140 mg of dicyclohexylcarbodiimide, 91 mg of hydroxybenzotriazole hydrate, and 10 mg of 4-dimethylaminopyridine at RT under N₂. The resultant mixture was stirred at RT overnight. The mixture was diluted with MeOH, filter through Celite®, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 90% acetonitrile and 10% dichloromethane with 0.5% to 1% H₂O as the gradient eluant afforded 90 mg of the title product of this example as a white solid. MS: 414 (M+1)⁺.

Example 38 4*H*-Benzo[*a*]quinolizin-4-one, 1,2,3,6,7,11b-hexahydro-9-hydroxy-11b-(phenylmethyl)-

A solution of 973 mg of 2-(3-hydroxyphenyl)ethylamine hydrobromide and 920 mg of 5-oxo-6-phenyl-hexanoic acid in 3 mL of isopropanol was heated to 210 °C open to the air for 5 h. The resultant residue was purified by flash chromatography over SiO₂ using 5% MeOH in dichloromethane to 20% MeOH in dichloromethane as the gradient eluant to afford 774 mg (56%) of the title product of this example as an off-white solid. MS: 307 (M+1)⁺.

Example 39 4*H*-Benzo[a]quinolizin-4-one, 1,2,3,6,7,11*b*-hexahydro-9-(phenylmethoxy)-11*b*-(phenylmethyl)-

To a stirring solution of 770 mg of the title product of Example 38 in DMF was added sequentially 3 mL of 1 M potassium *t*-butoxide in *t*-butanol followed by 0.35 mL of benzyl bromide. The reaction mixture was heated to 60 °C for 2 h. The mixture was cooled to room temperature and 1 N HCl was added. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 60% EtOAc in hexanes to 100% EtOAc as the gradient eluant afforded 797 mg (80%) of the title product of this example as an off-white solid. MS: 398 (M+1)⁺.

Example 40 2*H*-Benzo[a]quinolizine-3-carboxylic acid, 1,3,4,6,7,11*b*-hexahydro-4-oxo-9-(phenylmethoxy)-11*b*-(phenylmethyl)-3-propyl-, methyl ester, (3-*cis*)-

To a stirring solution of 0.61 mL of diisopropylamine in 9 mL of THF at 0 °C under N₂ was added 1.75 mL of 2.5 M *n*-butyl lithium in hexane. The resultant solution was stirred for 10 min. at 0 °C then cooled to -78 °C. To this solution was added 790 mg of the title product of Example 39 in 10 mL of THF dropwise over 30 min. The resultant solution was stirred at -78 °C for 30 min., warmed to 0 °C for 2 h, then cooled to -78 °C. To this solution was added 0.17 mL of methyl chloroformate. The resultant mixture was stirred for 30 min at -78 °C then warmed to RT and stirred for 1 h. To the reaction mixture was added 0.42 mL of propyl iodide and the resultant mixture was stirred at 0 °C for 1 h then warmed to RT for 14 h. To the reaction mixture was added an additional 0.5 mL of propyl iodide and the resultant mixture heated to 55 °C for 4 h. The mixture was poured into EtOAc and washed with 1 N HCl, H₂O, sat NaHCO₃, and brine. The organic solution was dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 40% EtOAc in hexanes as the eluant afforded 768 mg (78%) of the title product of this example as an off-white solid. MS: 498 (M+1)⁺.

Example 41 2*H*-Benzo[a]quinolizine-3-methanol, 1,3,4,6,7,11*b*-hexahydro-9-(phenylmethoxy)-11*b*-(phenylmethyl)-3-propyl-, (3-*cis*)-

To a stirring solution of 50 mg of the title product of Example 40 in 1 mL of THF was added 3 mL of 1.0 M lithium aluminum hydride in THF. The reaction mixture was heated to reflux under N₂ overnight. The mixture was cooled to 0 °C and

0.12 mL H₂O, 0.12 mL 15% NaOH, and 0.36 mL H₂O was added slowly and sequentially with stirring to the reaction mixture. After 5 min of rapid stirring, the mixture was filtered through Celite® and concentrated to dryness. Purification by flash chromatography over SiO₂ using 3% MeOH in dichloromethane to 10% MeOH in dichloromethane as the gradient eluant afforded 36 mg (79%) of the title product of this example as a white solid. MS: 456 (M+1)⁺.

Example 42 2*H*-Benzo[a]quinolizine-3-methanol, 1,3,4,6,7,11*b*-hexahydro-9-hydroxy-11*b*-(phenylmethyl)-3-propyl-, (3-*cis*)-

To a stirring solution of 31 mg of the title product of Example 41 in dichloromethane at -78 °C under N₂ was added 0.05 mL of BBr₃ and the reaction mixture allowed to warm to RT. The reaction mixture was cooled to -78 °C and MeOH was added dropwise to quench the reaction. The mixture was concentrated to dryness, dissolved in MeOH and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane with 0.1% triethylamine to 10 % MeOH in dichloromethane with 0.1% triethylamine as the gradient eluant afforded a white solid. This solid was partitioned between EtOAc and sat. NaHCO₃. The EtOAc layer was dried over Na₂SO₄, filtered, and concentrated to afford 10 mg of the title product of this example as a white solid. ¹H NMR (400 MHz, CD₃OD) δ 2.45 (d, 1H, J = 12), 2.66 (d, 1H, J = 12).

Example 43 2*H*-Benzo[a]quinolizine-3-carboxylic acid, 1,3,4,6,7,11*b*-hexahydro-9-hydroxy-4-oxo-11*b*-(phenylmethyl)-3-propyl-, methyl ester, (3-*cis*)-

A mixture of 50 mg of the title product of Example 40, 63 mg of ammonium formate, and 20 mg of 20% palladium hydroxide on carbon in 5 mL of MeOH was heated to reflux for 3 h. The mixture was cooled to RT, filtered through Celite®, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 50% EtOAc in hexanes as the eluant afforded 41 mg of the title product of this example as a white solid. MS: 408 (M+1)⁺.

Example 44 4*H*-Benzo[a]quinolizin-4-one, 1,2,3,6,7,11*b*-hexahydro-3-(hydroxymethyl)-9-(phenylmethoxy)-11*b*-(phenylmethyl)-3-propyl-, (3-*cis*)-

To a stirring solution of 50 mg of the title product of Example 40 in 5 mL of THF under N₂ was added 10 mg of lithium borohydride. The resultant mixture was

5 stirred for 2 h at RT then warmed to 40 °C and stirred an additional 2 h. After cooling to RT, sat. ammonium chloride was added and the mixture was extracted with EtOAc.

10 The EtOAc solution was dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 40% EtOAc in hexanes to 80% EtOAc in hexanes as the gradient eluant afforded 17 mg of the title product of this example as a white solid. MS: 470 (M+1)⁺.

15 Example 45 2(1*H*)-Phenanthrenone, 7-(acetyloxy)-3,4,4a,9,10,10a-hexahydro-4a-(phenylmethyl)-, (4a*S-trans*)-

To a stirring solution of 54 mg of the title compound of Example 6 in 2 mL of dichloromethane was added 0.037 mL of triethylamine and 0.015 mL of acetyl chloride and the resultant mixture was stirred overnight. The mixture was poured into 1 N HCl and extracted with dichloromethane. The dichloromethane solution was dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 20% EtOAc in hexanes as the eluant afforded 55 mg of the title product of this example. ¹H NMR (400 MHz, CDCl₃) δ 2.27 (s, 3H)

20 Example 46 1*H*-Benz[*e*]indene-2-carboxylic acid, 7-(acetyloxy)-2,3,3a,4,5,9b-hexahydro-9b-(phenylmethyl)-, [2*R*-(2α,3α,9bβ)]-

30 To a stirring solution of 50 mg of the title product of Example 45 in 1 mL of dichloromethane was added 75 mg of thallium trinitrate • 3H₂O under N₂ and the mixture stirred overnight. To the reaction mixture was added an additional 75 mg of thallium trinitrate • 3H₂O and the mixture was again stirred overnight. The mixture was filtered through Celite® and concentrated to afford the title product of this example as an off-white solid. MS: 363 (M-1)⁺.

25 Example 47 1*H*-Benz[*e*]indene-2-carboxylic acid, 2,3,3a,4,5,9b-hexahydro-7-hydroxy-9b-(phenylmethyl)-, methyl ester, [2*R*-(2α,3α,9bβ)]-

40 Continuing the procedure began in Example 46, a solution of the title product of Example 46 in methanol and catalytic sulfuric acid was heated to reflux under a soxlet extractor filled with 3 angstroms molecular sieves for 4 h. After cooling to RT, a small amount of solid NaHCO₃ was added to the solution, and it was concentrated to dryness. Purification by flash chromatography over SiO₂ using 20% EtOAc in

hexanes as the eluant afforded 28 mg of the title product of this example. MS: 335 (M-1)⁺.

Example 48 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-, [2*R*-(2α,4α,10aβ)]-

A solution of 50 mg of the title compound of Example 79 below (which was prepared by procedures described in Example 79), 54 mg of 1,2,4-triazole, and 108 mg of potassium carbonate in 4 mL of DMF was heated to 90 °C for 2 h. After cooling to RT, sat. ammonium chloride was added and the resultant mixture was extracted with EtOAc. The EtOAc solution was dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane as the eluant afforded 50 mg of the title product of this example as a white solid. MS: 391 (M+1)⁺.

Example 49 2(1*H*)-Phenanthrenone, 4a-(2-butenyl)-3,4,4a,5,8,9,10,10a-octahydro-7-methoxy-, [4a*S*-(4aα(*E*),10aβ)]-

Ammonia (200 mL) was condensed into a round bottom flask at -78 °C equipped with a dry ice reflux condenser at -78 °C and a mechanical stirrer. To this flask was added 80 mL of *t*-butanol followed by lithium wire until the solution turned dark blue. A solution of 5 g of 2(3*H*)-phenanthrenone, 4a-(2-butenyl)-4,4a,9,10-tetrahydro-7-methoxy-, [*S*-(*E*)]- in 80 mL of THF was added to the mixture slowly in order to keep the reaction a dark blue. As the blue color dissipated, a small amount of lithium wire was added to the mixture to regenerate the blue color. The total amount of lithium added to the reaction mixture did not exceed 4 g. After the complete addition of the starting compound the reaction was stirred an additional 40 min, then 100 mL of sat. ammonium chloride was added and immediate dissipation of the blue color was observed. H₂O was added to the mixture and it was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. The crude product was purified by flash chromatography over SiO₂ using 10% EtOAc to 25% EtOAc in hexanes as the gradient eluant to afford 2.0 g of the title product of this example as a white solid. MS: 287 (M+1)⁺.

Example 50 2-Phenanthrenol, 4a-(2-butenyl)-1,2,3,4,4a,5,8,9,10,10a-decahydro-7-methoxy-2-(1-propynyl)-, [2*R*-(2α,4aα(*E*),10aβ)]-

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To a stirring solution of 200 mL of THF saturated with propyne gas at 0 °C was added 16.4 mL of 2.5 M n-butyl lithium in hexane and the resultant mixture stirred under nitrogen atmosphere for 20 min. A solution of 1.96 g of the title product of Example 49 in 50 mL of THF was added dropwise, and the reaction mixture was warmed to RT and stirred for 40 min. Saturated, aqueous ammonium chloride was added, and the mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 10% EtOAc in hexanes to 15% EtOAc in hexanes as the eluant afforded 879 mg of the title product of this example as a white solid. MS: 327 (M+1)⁺.

Example 51 2(3*H*)-Phenanthrenone, 4b-(2-butenyl)-
4,4a,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-7-(1-propynyl)-,
[4a*R*-(4aα,4bβ(*E*),7β,8aα)]- and 2(1*H*)-Phenanthrenone, 4b-(2-
butenyl)-3,4,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-7-(1-
propynyl)-, [4b*S*-(4bα(*E*),7α,8aβ)]-

Continuing the procedures began in Example 50, to a stirring solution of the title product of Example 50 in 20 mL of THF was added 1 mL of 2 N HCl. After 3 h at RT, sat. NaHCO₃ was added and the mixture was extracted with EtOAc. The organic layer was dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 20% EtOAc in hexanes to 35% EtOAc in hexanes as the gradient eluant afforded 154 mg of the second listed title product of this example as a white solid. MS: 313 (M+1)⁺. Further purification of lower R_f material by flash chromatography over SiO₂ using 3% acetone in dichloromethane to 4% acetone in dichloromethane as the gradient eluant afforded 215 mg of the first listed title product of this example as a white solid. MS: 313 (M+1)⁺.

Example 52 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-
[(methylsulfonyl)oxy]phenyl]methyl]-2-propyl-, 7-
methanesulfonate, (4a*S*,10a*S*)-; and 2,7-Phenanthrenediol,
1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-[(methylsulfonyl)oxy]
phenyl]methyl]-2-propyl-, (4a*S*,10a*S*)-

To a stirring solution of 50 mg of 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-2-propyl-, (4a*S*,10a*S*)- in 0.039 mL of triethylamine and 3 mL of anhydrous THF was added slowly 0.011 mL of MeSO₂Cl at 0 °C under N₂ atmosphere. The reaction was allowed to warm to RT for 2 h, then quenched with water. The mixture was extracted with EtOAc (X3), washed with brine,

dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography over SiO₂ using 25% EtOAc in hexanes to 45% EtOAc in hexanes as the gradient eluant afforded 18 mg of the second listed title product of this example and 35 mg of the first listed title product of this example as white powder.

5 MS *m/z* 540 (M+ NH₄)⁺.

Example 53 1-Piperazinecarboxamide, *N*-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-4-methyl-, (4*aS*,10*aR*)-

To a stirring solution of 97 mg of carbamic acid, [4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, 1,1-dimethylethyl ester, [2*R*-(2*α*,4*α*,10*aβ*)]- in 0.078 mL of 1-methylpiperazine and 5 mL of anhydrous THF under N₂ atmosphere was added 0.56 mL of 2.5 M *n*-BuLi and the mixture was heated to 65 °C. After 2 h, the reaction was quenched with NH₄Cl (sat), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in CH₂Cl₂ as the elutant afforded 40 mg (40%) of the title product of this example as white fluffy powder. MS *m/z* 472 (M-Me)⁺.

Example 54 Acetic acid, [4-[[1,3,4,9,10,10a-hexahydro-2-hydroxy-7-(2-methoxy-2-oxoethoxy)-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenoxy]-, methyl ester, [2*R*-(2*α*,4*α*,10*aβ*)]-

A solution of 50 mg of 2,7-phenanthrenediol, 1,2,3,4,4*a*,9,10,10*a*-octahydro-4*a*-[[4-hydroxyphenyl]methyl]-2-(1-propynyl)-, [2*R*-(2*α*,4*α*,10*aβ*)]- in 5 mL anhydrous CH₃CN, 109.5 mg of Cs₂CO₃ and 0.067 mL of methyl bromoacetate was stirred at RT under N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by SiO₂ preparative TLC using 45% EtOAc in hexanes as the elutant afforded 20 mg (28%) of the title product of this example as white fluffy powder. MS *m/z* 489 (M-17)⁺.

Example 55 Acetamide, 2-[4-[[7-(2-amino-2-oxoethoxy)-1,3,4,9,10,10a-hexahydro-2-hydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenoxy]-, [2*R*-(2*α*,4*α*,10*aβ*)]-

A solution of 17 mg of the title product of Example 54 in 2 mL of NH₄OH (aq), 0.5 mL of toluene and 10 drops of MeOH was heated at 60 °C overnight. The

reaction was quenched with NH_4Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na_2SO_4 , filtered and concentrated to dryness. Purification by flash chromatography SiO_2 using 2% MeOH in CH_2Cl_2 to 4% MeOH in CH_2Cl_2 as the elutant afforded 5 mg (30%) of the title product of this example as white fluffy powder.

MS m/z 478 (M+H)⁺.

Example 56 2(1*H*)-Phenanthrenone, 4a-[[3-(dimethylamino)phenyl]methyl]-3,4,4a,9,10,10a-hexahydro-7-hydroxy-, (4a*S*-*cis*)-. See also Preparation 5 above.

Example 57 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-4a-[[4-(4*H*-1,2,4-triazol-4-yl)phenyl]methyl]-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

A solution of 50 mg of the title product of Example 776, below, 20 mg of dimethyl formamideazaine and 3 mg of *p*-toluenesulfonic acid in 5 mL of toluene was refluxed overnight. The reaction was quenched with NaHCO_3 (sat.), extracted with EtOAc (X3), washed with brine, dried over Na_2SO_4 , filtered and concentrated to dryness. Purification by flash chromatography SiO_2 using 1% MeOH in CH_2Cl_2 to 5% MeOH in CH_2Cl_2 as the elutant afforded 18 mg (31%) of the title product of this example as white fluffy powder. MS m/z 398 (M-Me)⁺.

Example 58 4-Morpholinecarboxylic acid, 7-(chloroethynyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-2-phenanthrenyl ester, (4b*S*,8a*R*)-

To a solution of 50 mg of 2,7-phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*S*-(2 α ,4 α ,10 $\alpha\beta$)]-, in 3 mL of anhydrous THF was added 0.019 mL of triethylamine, 1.7 mg of DMAP and followed by slow addition of 0.020 mL of 4-morpholinecarbonyl chloride at 0 °C under N_2 atmosphere. The reaction was warmed up to RT for 4 h and then quenched with NH_4Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na_2SO_4 , filtered and concentrated to dryness. Purification by flash chromatography SiO_2 using 2% EtOAc in hexanes to 30% EtOAc in hexanes as the gradient elutant afforded 57 mg (85%) of the title product of this example as white fluffy powder. MS m/z 480 (M)⁺.

Example 59 Carbamic acid, [2-(dimethylamino)ethyl]-, 4b-[[3-(dimethylamino)phenyl]methyl]-4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-

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A solution of 68 mg of 2,7-phenanthrenediol, 4a-[[3-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, (4a*S*,10a*R*)- in 64 mg of triphosgene, 0.03 mL of triethylamine and 2 mL of anhydrous dichloromethane was stirred at RT for 1.5 h under N₂ atmosphere. To the mixture, 0.099 mL of N, N-dimethylethylenediamine was added dropwise and stirred overnight under N₂ atmosphere. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography SiO₂ using 100% CHCl₃ and 0.1% of triethylamine to 2% EtOH in CHCl₃ and 0.1% of triethylamine as the gradient elutant afforded 20 mg (23%) of the title product of this example as white fluffy powder. MS *m/z* 504 (M+H)⁺.

Example 60 2-Phenanthrenol, 4a-[[3-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-7-(2-hydroxyethoxy)-2-(1-propynyl)-, [2*R*-(2α,4α,10aβ)]-

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To a solution of 76 mg of 2,7-phenanthrenediol, 4a-[[3-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, (4a*S*,10a*R*)- in 3 mL anhydrous DMF was added 1.4 mg of TBAI and 17 mg of ethylene carbonate, and the mixture was heated to 100 °C for 2 h. The reaction was quenched with water, extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography SiO₂ using 5% EtOAc in hexanes and 0.1% of triethylamine to 40% EtOAc in hexanes and 0.1% of triethylamine as the gradient elutant afforded 30 mg (36%) of the title product of this example as white fluffy powder. MS *m/z* 435 (M+H)⁺.

Example 61 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[(3-pyrazinyl-1,2,4-oxadiazol-5-yl)methoxy]-, [2*R*-(2α,4α,10aβ)]-

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To a solution of 29 mg of acetic acid, [[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, methyl ester, [4b*S*-(4bα,7α,8aβ)]- and 19.5 mg of pyrazine-2-carboxamide oxime in 3 mL of anhydrous THF was added 24 mg of NaH (60%) and refluxed overnight. The reaction was cooled to RT, filtered and concentrated to dryness. Purification by preparative TLC SiO₂ using 5% MeOH in dichloromethane as the elutant afforded 7 mg (20%) of the title product of this example. MS *m/z* 507 (M+H)⁺.

Example 62 2-Phenanthrenol, 7-[(5-amino-1*H*-1,2,4-triazol-3-yl)methoxy]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-
propynyl)-, (4a*S*,10a*R*)-

To a cooled (0 °C) solution of NaOMe prepared from 7 mg of sodium and 1
mL of anhydrous MeOH was added 40 mg of amino guanidine nitrate. Then 30 mg
acetic acid, [[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-
propynyl)-2-phenanthrenyl]oxy]-, methyl ester, [4b*S*-(4b α ,7 α ,8a β)]- in 1 mL of
anhydrous MeOH was added dropwise to the resultant mixture and refluxed under N₂
atmosphere overnight. The mixture was concentrated to dryness and purified with
preparative TLC using 10% MeOH in dichloromethane as the elutant to yield 11 mg
of the title product of this example (33%) as white fluffy powder. MS *m/z* 443 (M+H)⁺.

Example 63 Acetic acid, [[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-
(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-
(4b α ,7 α ,8a β)]-

A solution of 20 mg of acetic acid, [[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-
4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, methyl ester, [4b*S*-(4b α ,
7 α ,8a β)]- and 5.36 mg of KOH in 3 mL of MeOH and 0.5 mL of H₂O was heated at 80
°C for 4 h. The reaction was cooled to RT, extracted with EtOAc (X3), washed with
brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by a plug
of SiO₂ using 5% MeOH in CH₂Cl₂ as the elutant afforded 18 mg (93%) of the title
product of this example as white fluffy powder. MS *m/z* 387 (M-17)⁺.

Example 64 Acetonitrile, [[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-
(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-
(4b α ,7 α ,8a β)]-

To a solution of 54 mg of the first listed title product of Example 8 (which was
prepared by procedures analogous to those described in Example 8) and 8 mg of
60% NaH in 5 mL of anhydrous CH₃CN was added 0.056 mL bromoacetonitrile under
N₂ atmosphere. The reaction was heated to 85 °C overnight. The reaction was
quenched with NH₄Cl (sat), extracted with EtOAc (X3), washed with brine, dried over
Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography
SiO₂ using 0.5% acetone in CH₂Cl₂ to 1% acetone in CH₂Cl₂ as the gradient elutant
afforded 46 mg (76%) of the title product of this example as white fluffy powder. MS
m/z (M-17)⁺.

Example 65 2-Phenanthrenol, 7-(2-bromoethoxy)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2α,4α,10αβ)]-

To a solution of 5 mg of the first listed title product of Example 8 and 7 mg of 60% NaH in 5 mL of anhydrous CH₃CN was added 0.125 mL 1,2-dibromoethane under N₂ atmosphere. The reaction was heated to 85 °C overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography SiO₂ using 2% EtOAc in hexanes to 20% EtOAc in hexanes as the gradient elutant afforded 29 mg (44%) of the title product of this example as white fluffy powder. MS *m/z* 453 (M+H)⁺.

Example 66 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(1*H*-tetrazol-5-ylmethoxy)-, [2*R*-(2α,4α,10αβ)]- (Refer to Scheme B: B-7 → B-10)

A solution of 0.019 mL of TMSN₃ and 0.067 mL of Me₃Al in 5 mL of anhydrous toluene was stirred at 0 °C under N₂ atmosphere. To the resultant solution was added 43 mg of the title product of Example 64 in 1 mL of toluene slowly to keep the temperature below 5 °C. The reaction was then allowed to warm to RT and heated to 80 °C overnight. The reaction was cooled to 0 °C and quench with 5 mL of 10% HCl and 5 mL of EtOAc. The aqueous phase was acidified with 1 N HCl to pH around 3 and extracted with EtOAc (X3), dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography SiO₂ using 1% MeOH in CH₂Cl₂ and a couple of drops of AcOH to 10% MeOH in CH₂Cl₂ and a couple of drops of AcOH as the gradient elutant afforded 17 mg (36%) of the title product of this example as white fluffy powder. MS *m/z* 427 (M+H)⁺.

Example 67 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[2-(4-methyl-1-piperazinyl)ethoxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2α,4α,10αβ)]-

To a solution of 30 mg of the title product of Example 65 (which was prepared by procedures described in Example 65), 8 mg of anhydrous Na₂CO₃ and 12 mg of NaI in 2 mL of anhydrous DMF was added 0.015 mL of 1-methylpiperazine under N₂ atmosphere. The reaction was heated to 60 °C overnight. The reaction was quenched with NaHCO₃ (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC on

SiO₂ using 5% MeOH in methylene chloride as the elutant afforded 19 mg (60%) of the title product of this example as white fluffy powder. MS *m/z* 473 (M+H)⁺.

Example 68 Ethanimidamide, *N*-hydroxy-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-

To a solution of 30 mg of the title product of Example 64 and 22 mg of K₂CO₃ in 2 mL of anhydrous EtOH was added 8 mg of NH₂OH.HCl and heated to reflux for 6 h. The reaction was then concentrated to dryness and purified by preparative TLC using 5% MeOH in CH₂Cl₂ as the elutant to yield 11 mg of the title product of this example as white powder (34%). MS *m/z* 419 (M+H)⁺.

Example 69 2-Phenanthrenol, 7-[[5-[(dimethylamino)methyl]-1,2,4-oxadiazol-3-yl]methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10a β)]-

A solution of 30 mg of the title product of Example 68 (which was prepared by procedures described in Example 68) and 3 mg of 60% NaH in 3 mL of anhydrous THF was heated to 60 °C for 20 min. The solution was cooled to RT and 0.02 mL of ethyl-*N*, *N*-dimethyl glycine was added to the solution. The resultant mixture was heated to reflux for 1 h then cooled to RT, filtered and concentrated to dryness. Purification by preparative TLC using 10% acetone in CH₂Cl₂ and 0.05% of NH₄OH as the elutant yielded 4 mg of the title product of this example (11%). MS *m/z* 486 (M+H)⁺.

Example 70 1,2,4-Oxadiazol-5(2*H*)-one, 3-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]methyl]-, [4b*S*-(4b α ,7 α ,8a β)]-

To a solution of 30 mg of the title product of Example 68 (which was prepared by procedures described in Example 68), 0.006 mL of pyridine and 1 mL of anhydrous DMF in 2 mL of xylene was slowly added 0.014 mL of 2-ethyl hexyl chloroformate at 0 °C under N₂ atmosphere. After the reaction was stirred for 30 min, it was diluted with water, extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. The residue was dissolved in xylene and refluxed for 2 days. The mixture was then concentrated to dryness and purified by preparative TLC on SiO₂ using 5% MeOH in methylene chloride as the elutant to afford 6 mg (19%) of the title product of this example. MS *m/z* 443 (M+H)⁺.

Example 71 1,2,4-Oxadiazole-5(2H)-thione, 3-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]methyl]-, [4bS-(4b α ,7 α ,8a β)]-

To a solution of 20 mg of the title product of Example 68 (which was prepared by procedures described in Example 68) and 0.029 mL of DBU in 2 mL of anhydrous CH₃CN was added 14 mg of 1,1-thiocarbonyldiimidazole at RT and stirred for 1.5 h. The solution was diluted with water, adjusted to pH around 4 with 10% HCl, extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC on SiO₂ using 5% MeOH in methylene chloride as the elutant afforded 12 mg (54%) of the title product of this example as white fluffy powder. MS *m/z* 459 (M-H)⁺.

Example 72 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[[5-[2-(4-morpholinyl)ethyl]-1,2,4-oxadiazol-3-yl]methoxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2R-(2 α ,4 α ,10a β)]-

To a solution of 30 mg of the title product of Example 68 (which was prepared by procedures described in Example 68) and 3 mg of 60% NaH in 3 mL of anhydrous THF was added 0.023 mL of methyl 4-morpholine propionate and heated to reflux for 2 h. The solution was cooled, filtered, concentrated to dryness and purified by preparative TLC using 20% acetone in CH₂Cl₂ and a few drops of NH₄OH as the elutant to afford 14 mg of the title product of this example (36%) as white fluffy powder. MS *m/z* 542 (M+H)⁺.

Example 73 Carbamothioic acid, dimethyl-, S-[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl] ester, [4bS-(4b α ,7 α ,8a β)]-

A solution of 55 mg of carbamothioic acid, dimethyl-, O-[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl] ester, [4bS-(4b α ,7 α ,8a β)]- of in 2 mL of phenol ether was refluxed overnight under N₂ atmosphere. The solution was concentrated to dryness and purified by preparative TLC using 2% MeOH in CH₂Cl₂ as the elutant to yield 5 mg of the title product of this example. MS *m/z* 434 (M+H)⁺.

Example 74 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(pyrazinyloxy)-, [2R-(2 α ,4 α ,10a β)]-

To a solution of 30 mg of the first listed title product of Example 8 (which was prepared by procedures described in Example 8) and 4 mg of 60% NaH in 2 mL of anhydrous DMF was added 0.01 mL of chloropyrazine at 0 °C under N₂ atmosphere. The reaction was then heated to 60 °C for 2 h. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography SiO₂ using 2% EtOAc in hexanes to 25% EtOAc in hexanes as the gradient elutant afforded 20 mg (54%) of the title product of this example as white fluffy powder. MS *m/z* 426 (M+2)⁺.

Example 75 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[[2-(4-morpholinyl)-4-pyrimidinyl]oxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2α,4α,10aβ)]-

A solution of 12 mg of 2-phenanthrenol, 7-[(4-chloro-2-pyrimidinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2α,4α,10aβ)]- and 0.011 mL of morpholine in 2 mL of anhydrous THF was heated at

65°C overnight under N₂ atmosphere. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC SiO₂ using 50% EtOAc in hexanes as the elutant afforded 10 mg (75%) of the title product of this example as white fluffy powder. MS *m/z* 510 (M+H)⁺.

Example 76 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-

To a solution of 30 mg of the first listed title product of Example 8 (which was prepared by procedures described in Example 8) and 8 mg of 60% NaH in 2 mL of anhydrous DMF was added 18 mg of 3-picolyl chloride hydrochloride at RT under N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC SiO₂ using 4% MeOH in CH₂Cl₂ as the elutant afforded 32 mg (80%) of the title product of this example as white fluffy powder. MS *m/z* 438 (M+H)⁺.

Example 77 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-(phenylmethyl)-, *O*-ethyloxime

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To a solution of 150 mg of the first listed title product of Example 8 (which was prepared by procedures described in Example 8) and 80 mg of sodium acetate in 5 mL of EtOH was added 96 mg of O-ethylhydroxylamine hydrochloride and heated to 70 °C for 30 min. The solution was concentrated to dryness and purified by flash chromatography SiO₂ using 5% EtOAc in hexanes with 0.1% of Et₃N to 7% EtOAc in hexanes with 0.1% of Et₃N as the gradient elutant afforded 148 mg (86%) of the title product of this example as white fluffy powder. MS *m/z* 350 (M+H)⁺.

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Example 78 2-Phenanthrenol, 4b,5,6,7,8,8a,9,10-octahydro-4b-[(4-hydroxyphenyl)methyl]-7-propylidene-, [4b*S*-(4bα,7*Z*,8aα)]-

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A solution of 170 mg of propyltriphenylphosphonium bromide in 3 mL of anhydrous DMSO was added dropwise 0.44 mL of 1M sodium bis(trimethylsilane)amide in ether at RT under N₂ atmosphere for 10 min. To the resultant solution was added 35 mg of the title product of Preparation 17 in 1.5 mL DMSO dropwise and the mixture was heated at 70 °C overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography SiO₂ using 10% EtOAc in hexanes to 25% EtOAc in hexanes as the gradient elutant afforded 34 mg (89%) of the title product of this example as white fluffy powder. MS *m/z* 349 (M+H)⁺.

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Example 79 Spiro[oxirane-2,2'(1'*H*)-phenanthren]-7'-ol, 3',4',4'a,9',10',10'a-hexahydro-4'a-(phenylmethyl)-, [2'*R*-(2'α,4'α,10'aβ)]-

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To a solution of 91 mg of trimethyl sulfonium iodide in 1 mL of anhydrous DMF was added 55 mg of *t*-BuOK at 0 °C under N₂ atmosphere and the mixture was stirred for 5 min. To the resultant solution was added 20 mg of the title product of Example 6 in 1 mL of DMF slowly and stirred for another 1 h at 0 °C. The reaction was quenched with NH₄Cl (sat), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by flash chromatography SiO₂ using 100% CH₂Cl₂ to 2% acetone in CH₂Cl₂ as the gradient elutant afforded 13 mg (70%) of the title product of this example as white fluffy powder. MS *m/z* 303 (M-17)⁺.

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Example 80 2-Phenanthreneacetonitrile, 1,2,3,4,4a,9,10,10a-octahydro-2,7-dihydroxy-4a-(phenylmethyl)-, (4a*S*,10a*R*)-, -2*R*-,

A solution of 9 mg of the title product of Example 79 and 22 mg of potassium cyanide in 1 mL of ethylene glycol was heated at 100 °C for 2 h. The reaction was

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Example 84 Piperidine, 4-[[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]methyl]-1-(methylsulfonyl)-, [2*R*-(2 α ,4 α ,10 α)]-, m.p. = 124-127°C.

Example 85 Piperidine, 4-[[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]methyl]-1-(ethylsulfonyl)-, [2*R*-(2 α ,4 α ,10 α)]-, m.p. = 174-176°C.

Example 86 Piperidine, 4-[[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]methyl]-1-(2-thienylsulfonyl)-, [2*R*-(2 α ,4 α ,10 α)]-, m.p. = 145-148°C.

Examples 87-90

The following compounds were prepared by using methods analogous to those described in Example 35 above.

Example 87 Benzoic acid, 4-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]-, methyl ester, [2*R*-(2 α ,4 α (*E*),10 α)]-, m.p. = 199-208°C (dec).

Example 88 Benzoic acid, 3-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]-, methyl ester, [2*R*-(2 α ,4 α (*E*),10 α)]-, m.p. = 93-95°C.

Example 89 4-Thiazolecarboxylic acid, 2-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]-, ethyl ester, [2*R*-(2 α ,4 α (*E*),10 α)]-, MS: 472.

Example 90 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-[4-(hydroxymethyl)phenyl]-2-propenyl]-, [2*R*-(2 α ,4 α (*E*),10 α)]-, MS: 405 (M-18)*.

Example 91 Benzoic acid, 4-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]-, [2*R*-(2 α ,4 α (*E*),10 α)]-

To a stirred solution of the title compound of Example 87 in methanol (9 mL) was added a solution of potassium hydroxide (250mg) in water (0.6mL) and the resulting solution was refluxed for 3 h. The reaction was allowed to cool to room temperature, saturated aqueous ammonium chloride was added and the mixture was extracted with ethyl acetate (3x). The combined organic layers were dried over

magnesium sulfate and concentrated in vacuo to afford the title compound of this example as an off-white solid, 381 mg. mp 145-146 °C (dec).

Example 92 Morpholine, 4-[4-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]benzoyl]-, [2*R*-[2α,4α(*E*),10aβ]]-

To a stirred solution of the title product of Example 91 (100 mg) and N-hydroxysuccinimide (26 mg) in dioxane (2.3 mL) at 0 °C was 1,3-dicyclohexylcarbodiimide (47 mg) and the resulting solution was allowed to warm to room temperature and stirred for 3 h. Acetonitrile (10 mL) was added and the resulting slurry was filtered through Celite®. Concentration of the filtrate afforded an oil (170 mg), which slowly crystallized upon standing. The solid residue and morpholine (0.08mL) were suspended in acetonitrile (3.5 mL) and heated at 50 °C for 3 h. Saturated aqueous ammonium chloride was added, extracted with ethyl acetate (3x), the organic layers combined, dried over sodium sulfate and concentrated in vacuo to afford a foam. Flash chromatography on silica gel (1:1 to 3:1 ethyl acetate:hexanes) afforded the title compound of this example as an off-white foam, 60mg. m.p. = 129-136 °C, MS: 506.

Examples 93-100

The following styryl amide compounds were prepared using procedures analogous to those described above in Examples 91 and 92.

Example 93 Piperazine, 1-[4-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]benzoyl]-4-methyl-, [2*R*-[2α,4α(*E*),10aβ]]-MS: 519

Example 94 4-Piperidinol, 1-[4-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]benzoyl]-, [2*R*-[2α,4α(*E*),10aβ]]-MS: 520

Example 95 Benzamide, 4-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]-, [2*R*-[2α,4α(*E*),10aβ]]-MS: 436

Example 96 Benzoic acid, 3-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]-, [2*R*-[2α,4α(*E*),10aβ]]-m.p. = 101-105 °C

- Example 97 Morpholine, 4-{3-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2H)-phenanthrenyl]-1-propenyl]benzoyl}-, [2*R*-[2 α ,4 α (*E*),10a β]]-m.p. = 135-141 °C
- Example 98 Piperazine, 1-[3-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2H)-phenanthrenyl]-1-propenyl]benzoyl]-4-methyl-, [2*R*-[2 α ,4 α (*E*),10a β]]- MS: 519
- Example 99 4-Piperidinol, 1-[3-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2H)-phenanthrenyl]-1-propenyl]benzoyl]-, [2*R*-[2 α ,4 α (*E*),10a β]]-MS: 520
- Example 100 Morpholine, 4-[[2-[3-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2H)-phenanthrenyl]-1-propenyl]-4-thiazolyl]carbonyl]-, [2*R*-[2 α ,4 α (*E*),10a β]]-MS: 513
- Example 101 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-[4-(hydroxymethyl)phenyl]-2-propenyl]-, 7-acetate, [2*R*-[2 α ,4 α (*E*),10a β]]-

To a stirred solution of 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-[4-(*t*-butyldimethylsiloxyethyl)phenyl]-2-propenyl]-, [2*R*-[2 α ,4 α (*E*),10a β]]- (322mg), tetrabutylammonium hydroxide (0.7 mg) and sodium hydroxide (60 mg) in dioxane (1 mL) at 5 °C was added dropwise a solution of acetyl chloride (57 mg) in dioxane (1 mL). The reaction was allowed to warm to room temperature and stirred for 2 h. An additional portion of acetyl chloride (57 mg) was added and stirring was continued an additional 2 h. The reaction was quenched with aqueous ammonium chloride, extracted with ethyl acetate, the organic phase dried over sodium sulfate and the filtrate concentrated in vacuo. Flash chromatography on silica gel (10 to 20% ethyl acetate/hexanes) afforded an oil, 91 mg. To a cooled (0 °C), stirred solution of this oil in tetrahydrofuran (1.6 mL) was added a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (0.23 mL). After 2 h, the reaction was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, the organic layer dried over sodium sulfate, concentrated and flash chromatographed on silica gel (10-50% ethyl acetate/hexanes) to afford the title compound of this example, 22 mg. mp 73-77 °C.

Example 102 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-[4-(4-morpholinylmethyl)phenyl]-2-propenyl]-, 7-acetate, [2*R*-[2 α ,4 α (*E*),10 α β]]-

To a cooled (0 °C), stirred solution of the title product of Example 101 (40 mg) (which was prepared by procedures described in Example 101) in tetrahydrofuran (0.9 mL) were added sequentially methanesulfonyl chloride (39 mg) and diisopropylethylamine (33 mg). After 2 h, the reaction was cooled to -78 °C, morpholine (0.12mL) was added and the reaction solution was allowed to warm to 0 °C. After 4 h, the reaction was quenched with aqueous ammonium chloride, extracted with ethyl ether, dried over sodium sulfate and concentrated in vacuo to afford a gum. Flash chromatography on silica gel (40-75% ethyl acetate/hexanes) afforded the title compound of this example as a colorless gum, 35 mg: MS: 534

Example 103 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-[4-(4-morpholinylmethyl)phenyl]-2-propenyl]-, [2*R*-[2 α ,4 α (*E*),10 α β]]-

To a suspension of the title product of Example 102 (25 mg) in methanol (0.5 mL) and water (0.25 mL) was added saturated aqueous sodium bicarbonate (0.25 mL) and the reaction mixture was allowed to stir at room temperature for 2 h. The reaction was quenched with saturated aqueous ammonium chloride, extracted with ethyl acetate, the organic phase was dried over sodium sulfate and concentrated in vacuo to afford a colorless solid. Flash chromatography on silica gel (50-100% ethyl acetate/hexanes) afforded the title compound of this example as a colorless solid, 15 mg: MS: 492

Examples 104-106

The following aminomethyl substituted styryl compounds were prepared using procedures analogous to those described above in Examples 101-103.

Example 104 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-[4-[(4-hydroxy-1-piperidiny)lmethyl]phenyl]-2-propenyl]-, 7-acetate, [2*R*-[2 α ,4 α (*E*),10 α β]]-MS: 548

Example 105 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-[4-[(4-hydroxy-1-piperidiny)lmethyl]phenyl]-2-propenyl]-, [2*R*-[2 α ,4 α (*E*),10 α β]]-MS: 506

Example 106 2,7-Phenanthrenediol, 2-(chloroethynyl)-4a-[3-[4-[(dimethylamino)methyl]phenyl]-2-propenyl]-

1,2,3,4,4a,9,10,10a-octahydro-, [2*R*-(2α,4α(*E*),10aβ)]-MS:
450.

Example 107 Carbamic acid, dimethyl-, 4b-[2-(4-formylphenoxy)ethyl]-
4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-
phenanthrenyl ester, [4b*S*-(4bα,7α,8aβ)]-

To a stirred solution of the title product of Preparation 10 (1.9 g) in pyridine (50 mL) was added p-toluenesulfonyl chloride (2.0 g). After 18 h at room temperature, the reaction solution was partitioned between ethyl ether and 0.5 N aqueous sodium hydrogensulfate, the aqueous phase extracted with additional ethyl ether (2x), the combined organic layers dried over sodium sulfate, concentrated in vacuo and flash chromatographed on silica gel (50-60% ethyl acetate/hexanes) to afford a colorless foam, 1.5 g. To a solution of this oil in dimethylformamide (9 mL) was added a solution of p-hydroxybenzaldehyde (0.44 g) and potassium t-butoxide (1 M in tetrahydrofuran, 3.3 mL) in dimethylformamide (5 mL, stirred at ambient temperature for 0.5 h) and the resulting solution was heated at 80 °C for 4 h. The reaction was cooled, diluted into ethyl ether, washed with water, brine, dried over sodium sulfate and concentrated in vacuo. The resulting oil was flash chromatographed to afford the title compound of this example as a colorless foam, 1.3 g. MS: 476 (M+1)*.

Example 108 Carbamic acid, dimethyl-, 4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-4b-[2-[4-(4-morpholinylmethyl)phenoxy]ethyl]-7-(1-
propynyl)-2-phenanthrenyl ester, [4b*S*-(4bα,7α,8aβ)]-, HCl salt

A solution of the title product of Example 107 (50 mg), acetic acid (7 mg), morpholine (18 mg) and sodium triacetoxyborohydride (33 mg) in 1,2-dichloroethane (2 mL) was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous sodium bicarbonate, extracted with dichloromethane, the organic phase was dried over sodium sulfate and concentrated in vacuo to afford an oil. Flash chromatography on silica gel (ethyl acetate) afforded the title compound of this example as colorless foam, 50 mg. MS: 547.

Examples 109-129

The following examples were prepared using procedures analogous to those described above in Examples 107 and 108.

Example 109 Carbamic acid, dimethyl-, 4b-[2-[4-
[(dimethylamino)methyl]phenoxy]ethyl]-4b,5,6,7,8,8a,9,10-

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Example 110

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Example 111

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Example 112

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Example 113

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Example 114

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Example 115

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Example 116

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Example 117

octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl
ester, [4bS-(4b α ,7 α ,8a β)]-, HCl salt, MS: 505

Carbamic acid, dimethyl-, 4b-[2-[4-
[(ethylamino)methyl]phenoxy]ethyl]-4b,5,6,7,8,8a,9,10-
octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl
ester, [4bS-(4b α ,7 α ,8a β)]-, HCl salt, MS: 505

Carbamic acid, dimethyl-, 4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-4b-[2-[4-[(methylamino)methyl]phenoxy]ethyl]-7-(1-
propynyl)-2-phenanthrenylester, [4bS-(4b α ,7 α ,8a β)]-, HCl salt,
MS: 491

Carbamic acid, dimethyl-, 4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-4b-[2-[4-[[methyl(methylsulfonyl)amino]methyl]
phenoxy]ethyl]-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-
(4b α ,7 α ,8a β)]-, m.p. 82-85 °C

Carbamic acid, dimethyl-, 4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-7-(1-propynyl)-4b-[2-[4-(1-
pyrrolidinylmethyl)phenoxy]ethyl]-2-phenanthrenyl ester, [4bS-
(4b α ,7 α ,8a β)]-, HCl salt, MS: 531

Carbamic acid, dimethyl-, 4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-4b-[2-[4-[(4-methyl-1-
piperazinyl)methyl]phenoxy]ethyl]-7-(1-propynyl)-2-
phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-, HCl salt, MS: 560

Carbamic acid, dimethyl-, 4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-4b-[2-[4-[[methyl(1-methyl-4-
piperidinyl)amino]methyl]phenoxy]ethyl]-7-(1-propynyl)-2-
phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-, HCl salt, MS: 588

Carbamic acid, dimethyl-, 4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-4b-[2-[4-[[2-
methoxyethyl]amino]methyl]phenoxy]ethyl]-7-(1-propynyl)-2-
phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-, HCl salt, MS: 535

Carbamic acid, dimethyl-, 4b-[2-[4-[[2-
(dimethylamino)ethyl]amino]methyl]phenoxy]ethyl]-

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Example 118

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Example 119

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Example 120

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Example 121

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Example 122

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Example 123

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Example 124

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Example 125

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4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, HCl salt, MS: 548

Carbamic acid, dimethyl-, 4b-[2-[4-[[[2-(dimethylamino)ethyl]methylamino]methyl]phenoxy]ethyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, HCl salt, MS: 562

Carbamic acid, dimethyl-, 4b-[2-[4-[[[diethylamino)methyl]phenoxy]ethyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, HCl salt, MS: 533

Carbamic acid, dimethyl-, 4b-[2-[4-[[[cyclopropylamino)methyl]phenoxy]ethyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, HCl salt, MS: 517

Carbamic acid, dimethyl-, 4b-[2-[4-[[[bis(2-methoxyethyl)amino)methyl]phenoxy]ethyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, HCl salt, MS: 593

2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[2-[4-(4-morpholinylmethyl)phenoxy]ethyl]-, [2*R*-(2 α ,4 α ,10a β)]-, MS: 496

Carbamic acid, dimethyl-, 7-(chloroethynyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-[2-[4-(4-morpholinylmethyl)phenoxy]ethyl]-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, HCl salt, MS: 567

2,7-Phenanthrenediol, 2-(chloroethynyl)-4a-[2-[4-[[[dimethylamino)methyl]phenoxy]ethyl]-1,2,3,4,4a,9,10,10a-octahydro-, [2*R*-(2 α ,4 α ,10a β)]-, MS: 454

Carbamic acid, dimethyl-, 7-(chloroethynyl)-4b-[2-[4-[[[dimethylamino)methyl]phenoxy]ethyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, HCl salt, MS: 525

- Example 126 Sulfamic acid, dimethyl-, 7-(chloroethynyl)-4b-[2-[4-
[(dimethylamino)methyl]phenoxy]ethyl]-4b,5,6,7,8,8a,9,10-
octahydro-7-hydroxy-2-phenanthrenyl ester, [4b*S*-
(4b α ,7 α ,8a β)]-, HCl salt, MS: 561
- 5 Example 127 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-
octahydro- 4a-[2-[4-(hydroxymethyl)phenoxy]ethyl]-, [2*R*-
(2 α ,4 α ,10a β)]-, m.p. = 179-186 °C
- 15 Example 128 Benzaldehyde, 4-[2-[2-(chloroethynyl)-1,3,4,9,10,10a-
hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]ethoxy]-, [2*R*-
(2 α ,4 α ,10a β)]-, MS: 407 (M-18)*
- 20 Example 129 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-
octahydro-4a-(2-phenoxyethyl)-, [2*R*-(2 α ,4 α ,10a β)]-, MS: 379
(M-18)*
- 25 Example 130 Naphtho[1,2-*d*]thiazol-7-ol, 2-amino-7-(chloroethynyl)-
4,5,5a,6,7,8,9,9a-octahydro-9a-(phenylmethyl)-, [5a*R*,*S*-
(5a α ,7 β ,9a β)]-
- 30 A solution of the title product of Preparation 14 (46 mg) and thiourea (22 mg)
in acetonitrile (2 mL) were heated at reflux for 8 h. The reaction was concentrated in
vacuo, partitioned between sat. aqueous sodium bicarbonate and chloroform, the
organic layer dried over sodium sulfate, concentrated in vacuo and flash
chromatographed on silica gel (40% ethyl acetate/hexanes) to afford a colorless
solid, 25 mg. Addition of lithio-2-chloroethyne was carried out using the general
procedure described above in Example 8 to afford the title compound of this example
as a tan solid, 7 mg. MS: 373
- 35 Example 131 Formamide, *N*-[7-(chloroethynyl)-4,5,5a,6,7,8,9,9a-octahydro-
7-hydroxy-9a-(phenylmethyl)naphtho[1,2-*d*]thiazol-2-yl]-,
[5a*R*,*S*-(5a α ,7 β ,9a β)]-
- 40 Using procedures analogous to those described in Preparations 11-14 and
Example 130 above, except dimethylformamide was substituted in the thiourea
cyclization reaction to afford the corresponding *N*-formyl derivative, which is the title
product of this example. MS: 401
- 45 Example 132 2*H*-Benz[*g*]indazol-7-ol, 7-(chloroethynyl)-4,5,5a,6,7,8,9,9a-
octahydro-9a-(phenylmethyl)-, [5a*R*,*S*-(5a α ,7 β ,9a β)]-
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5 A solution of the title product of Preparation 15 (244 mg) and hydrazine (75
10 mg) in ethanol (7 mL)/water (1 mL) was stirred at room temperature for 16 h. The
reaction was diluted into ethyl acetate, washed with water, brine, dried over sodium
sulfate and flash chromatographed to afford a colorless foam, 190 mg. To this foam
5 was added a solution of ethanol (10 mL), 20% sulfuric acid/water (v/v) and the
resulting solution was refluxed for 5 h. The reaction was diluted into ethyl ether,
15 washed with sat. aqueous sodium bicarbonate, brine, dried over sodium sulfate and
concentrated in vacuo to afford a golden oil. Addition of lithio-2-chloroethyne was
carried out using the general procedure described above in Example 8 to afford the
20 title compound of this example as a tan foam, 129 mg. MS: 341

Example 133 2H-Benz[g]indazol-7-ol, 7-(chloroethynyl)-4,5,5a,6,7,7,9,9a-
octahydro-9a-(phenylmethyl)-, [5aR,S-(5a α ,7 β ,9a α)]-

The title compound of this example was prepared by procedures analogous to
those described above in Example 132. MS: 341.

25 Example 134 Benzo[h]quinazolin-8-ol, 2-amino-8-(chloroethynyl)-
5,6,6a,7,8,9,10,10a-octahydro-10a-(phenylmethyl)-, [6aR,S-
(6a α ,8 β ,10a β)]-

30 A solution of sodium metal (25 mg) in isopropyl alcohol (1.5 mL) and
guanidine sulfate (107 mg) were refluxed for 1h, then the title product of Preparation
20 15 (154 mg) was added and refluxing was continued for 24 h. Work-up and
subsequent elaboration according to procedures analogous to those described in
Example 132 afforded the title compound of this example as a colorless foam, 43 mg.
35 MS: 368

Example 135 2-Phenanthrenol, 2-(chloroethynyl)-2,3,4,4a,9,10-hexahydro-7-
25 methoxy-4a-(phenylmethyl)-, (2*R*-cis)-

40 The title compound of this example was prepared by procedures analogous to
those described above in Example 8. MS: 361 (M-17)⁺.

Example 136 2-Phenanthrenol, 2,3,4,4a,9,10-hexahydro-7-methoxy-2-
phenyl-4a-(phenylmethyl)-, (2*R*-cis)-

45 30 To a flame dried flask, 5 ml of THF and 1.3 ml of phenylmagnesium chloride
were added. The title product of Example 3 (200 mg) in 5 ml THF was added
dropwise to the solution (sat.) at 0 °C. The reaction was stirred at 0 °C for an hour
and quenched with NH₄Cl extracted with EtOAc, dried over Na₂SO₄ and filtered. The
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mixture was purified with flash chromatography (25% EtOAc in hexane) on silica gel to afford the title product of this example as light yellow solid, 245 mg, yield 98%, MS:

379 (M-17)⁺.

Example 137 2,7-Phenanthrenediol, 2,3,4,4a,9,10-hexahydro-2,4a-bis(phenylmethyl)-, (2*S*-*cis*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 136. MS: 379 (M-17)⁺.

Example 138 2,7-Phenanthrenediol, 2,3,4,4a,9,10-hexahydro-4a-(phenylmethyl)-2-(2-pyridinyl)-, (2*R*-*cis*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 383 (M+1)⁺.

Example 139 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-(4-nitrophenoxy)-4a-(phenylmethyl)-, (*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. MS: 426 (M+1)⁺.

Examples 140-143

The title compounds of Examples 140-143 were prepared by procedures analogous to those described above in Example 136.

Example 140 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1,2-propadienyl)-, (4a*S*,10a*R*)-, MS: 329 (M-17)⁺.

Example 141 2,7-Phenanthrenediol, 2,3,4,4a,9,10-hexahydro-2-(2-naphthalenylmethyl)-4a-(phenylmethyl)-, (4a*S*)-, MS: 429 (M-17)⁺.

Example 142 2,7-Phenanthrenediol, 2,3,4,4a,9,10-hexahydro-2-(2-naphthalenylmethyl)-4a-(phenylmethyl)-, (4a*S*)-, MS: 429 (M-17)⁺.

Example 143 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2,4a-bis(phenylmethyl)-, (4a*S*)-, MS: 416 (M+18)⁺.

Example 144 2,7-Phenanthrenediol, 2-(chloroethynyl)-2,3,4,4a,9,10-hexahydro-4a-(phenylmethyl)-, (2*R*-*cis*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 8. MS: 347 (M-17)⁺.

Example 145 2,7-Phenanthrenediol, 2-ethynyl-2,3,4,4a,9,10-hexahydro-4a-(phenylmethyl)-, (2*R*-*cis*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 5. MS: 313 (M-17)⁺.

Examples 146-147

The title compounds of Examples 146-147 were prepared by procedures analogous to those described above in Example 136.

Example 146 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-phenyl-4a-(phenylmethyl)-, (4a*S*,10a*R*)-, MS: 367 (M-17)⁺.

Example 147 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-phenyl-4a-(phenylmethyl)-, (4a*S*,10a*R*)-, MS: 367 (M-17)⁺.

Example 148 2,7-Phenanthrenediol, 2-ethynyl-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 350 (M+18)⁺.

Example 149 2,7-Phenanthrenediol, 2-cyclopropyl-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above Example 136. MS: 331 (M-17)⁺.

Example 150 2,7-Phenanthrenediol, 2-(cyclopropylethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above Example 9. MS: 355 (M-17)⁺.

Example 151 2,7-Phenanthrenediol, 2-butyl-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, (4a*S*,10a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 136. MS: 382 (M+18)⁺.

Examples 152-153

The title compounds of Examples 152-153 were prepared by procedures analogous to those described above in Example 9.

Example 152 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(2-thienyl)-, (4a*S*,10a*R*)-, MS: 373 (M-17)⁺.

Example 153 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(2-pyridinyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 386 (M+1)⁺.

Example 154 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 6. MS: 309 (M+1)⁺.

Example 155 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*S*-(2 α ,4 α ,10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 8. MS: 349 (M-17)⁺.

Example 156 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(3,3,3-trifluoro-1-propynyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

A 5-L three-necked, round-bottom flask was equipped with a dry ice condenser and a dropping funnel. The flask was charged with 1000 mL anhydrous THF, and 3,3,3-trifluoropropyne gas was bubbled through for 10 mins. About 100 g (~15 eqs) of the gas was condensed during this period. Solution was then cooled to -78 °C and 200 mL of n-BuLi (2.5 M solution in hexanes, ~8 eqs) was added slowly via the dropping funnel. The resultant mixture was stirred under -78 °C for 1 hour. Then 300 mL of anhydrous THF was added to the reaction flask. A solution of 20 g of the starting compound, 2(1*H*)-phenanthrenone, 4a-(benzyl)-3,4,4a,5,8,9,10,10a-octahydro-7-hydroxy-, [4a*S*-(4 $\alpha\alpha$ [E], 10 $\alpha\beta$)]- in 200 mL of THF was added dropwise, followed by the addition of another 500 mL anhydrous THF, and the reaction mixture was stirred at -78 °C for another hour. Saturated, aqueous ammonium chloride solution was added and the mixture was extracted with EtOAc three times, dried and concentrated. Purification by flash chromatography over SiO₂ using 2% Ethyl Acetate in Methylene Chloride to 5% Ethyl Acetate in Methylene Chloride as the eluant afforded 20.8 g of the title product of this example as a yellow-white solid. MS : 399 (M-1)⁺.

Example 157 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-(phenylmethyl)-, (4a*R*-*cis*)-

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The title compound of this example was prepared by procedures analogous to those described above in Example 7. MS: 307 (M+1)⁺.

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Examples 158-159

The title compounds of Examples 158-159 were prepared by procedures analogous to those described above in Example 8.

Example 158 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*S*-(2α,4α,10α)]-, MS: 349 (M-17)⁺.

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Example 159 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2α,4aβ,10aβ)]-, MS: 349 (M-17)⁺.

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Example 160 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(2-thiazolyl)-, (4a*S*,10a*R*)-

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The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 392 (M+1)⁺.

Example 161 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2α,4aβ,10aα)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 8. MS: 349 (M-17)⁺.

Example 162 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*S*-(2α,4aβ,10aβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 349 (M-17)⁺.

Examples 163-164

The title compounds of Examples 163-164 were prepared by procedures analogous to those described above in Example 8.

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Example 163 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2α,4α,10α)]-, MS: 349 (M-17)⁺.

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Example 164 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*S*-(2α,4aβ,10aβ)]-, MS: 349 (M-17)⁺.

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Example 165 2-Phenanthrenecarbonitrile, 1,2,3,4,4a,9,10,10a-octahydro-2,7-dihydroxy-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

At room temperature and under nitrogen atmosphere, 159 mg of KCN was added into 75 mg of the title product of example 6 in methanol (4 ml) and followed by 0.070 mL of HOAc. The mixture was stirred overnight at room temperature, quenched with NaHCO₃ (sat.) , extracted with EtOAc, dried over Na₂SO₄, filtered and concentrated to dryness. The crude product was purified with column chromatography with 0.5% acetone in CH₂Cl₂ as the eluant to yield 20.4 mg of the title product of this example as white solid. MS: 322 (M+1) ¹³C NMR (100 MHz, CD₃OD) δ; 24.8, 27.8, 33.6, 36.0, 37.6, 39.3, 43.6, 44.0, 74.6, 111.3, 114.6, 125.6, 126.8, 127.0, 127.9, 130.7, 133.8, 136.8, 138.0, 155.1.

Example 166 2-Phenanthrenecarbonitrile, 1,2,3,4,4a,9,10,10a-octahydro-2,7-dihydroxy-4a-(phenylmethyl)-, (4a*S*,10a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 165. ¹³C NMR (100 MHz, CD₃OD) δ; 26.2, 29.3, 35.1, 37.4, 39.1, 41.6, 45.1, 45.5, 71.5, 112.7, 116.0, 127.1, 128.3, 128.4, 129.4, 132.1, 134.9, 138.6, 139.5, 156.5.

Example 167 2-Phenanthrenecarbonitrile, 1,2,3,4,4a,9,10,10a-octahydro-7-[[[(4-methylphenyl)sulfonyl]oxy]-4a-(phenylmethyl)-, (4a*S*,10a*R*)-

Tosyl chloride (0.13 mL) was added slowly to a stirring solution of 106 mg of the corresponding phenol in 0.1 mL of triethylamine and 1 mL of anhydrous CH₂Cl₂ at 0 °C under nitrogen atmosphere. The reaction was allowed to warm to room temperature for 4 h, then 40 °C overnight. It is quenched with water. The mixture was extracted with CH₂Cl₂ (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification with flash chromatography over SiO₂ using 20% EtOAc in hexanes as the eluant afforded 63 mg of pure title product of this example as white crystalline solid. MS: 489 (M+18)⁺.

Example 168 2,7-Phenanthrenediol, 4a-(2,3-dihydroxypropyl)-1,2,3,4,4a,9,10,10a-octahydro-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 6. IR (neat) 3380, 2929, 1612 cm⁻¹.

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Example 169 Acetamide, *N*-[5-[3-(3,4,9,10-tetrahydro-7-methoxy-2-oxo-4a(2*H*)-phenanthrenyl)-1-propenyl]-2-pyridinyl]-, [*S*-(*E*)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 35. MS: 403 (*M*+1)⁺.

5 Example 170 2-Phenanthrenecarbonitrile, 1,2,3,4,4a,9,10,10a-octahydro-7-hydroxy-4a-(phenylmethyl)-, (4a*S*,10a*R*)-

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The title product of Example 167 (20 mg) and KOH (38 mg) in EtOH (0.7 ml) and water (0.7 ml) were mixed. The mixture was refluxed overnight, then neutralized with HOAc, extracted with EtOAc, dried and concentrated to dryness. The crude mixture was purified with column chromatography with 5% isopropanol in hexane as the eluant to yield 1.2 mg of the pure title product of this example as the white solid. MS: 318 (*M*+1)⁺.

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The title compounds of Examples 171-174 were prepared by procedures analogous to those described above in Example 8.

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15 Example 171 Acetamide, *N*-[5-[3-[2-(chloroethynyl)-3,4,9,10-tetrahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-propenyl]-2-pyridinyl]-, [*2R*,4a(*E*)]-, MS: 449 (*M*+1)⁺.

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Example 172 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(2-propenyl)-, [*2R*-(2α,4α,10aβ)]-, ¹H NMR (400 MHz, CD₃OD) δ 4.90-4.97 (m, 2H), 5.45-5.61 (m, 1H), 6.51-6.53 (m, 2H), 6.95 (d, 1H, *J* = 9).

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Example 173 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(2-propenyl)-, [*2S*-(2α,4aβ,10aα)]-, ¹H NMR (400 MHz, CD₃OD) δ 4.90-4.96 (m, 2H), 5.53-5.60 (m, 1H), 6.48-6.51 (m, 2H), 6.93 (d, 1H, *J* = 9)

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Example 174 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(2-propenyl)-, [*2S*-(2α,4aβ,10aβ)]-, ¹H NMR (400 MHz, CD₃OD) δ 4.87-5.46 (m, 2H), 5.70-5.80 (m, 1H), 6.50 (d, 1H, *J* = 2.7), 6.57 (dd, 1H, *J* = 2.7, 8.5), 7.04 (d, 1H, *J* = 8.5).

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30 Example 175 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-hydroxy-4a-(2-propenyl)-, (*S*)-, ¹H NMR (400 MHz, CD₃OD) δ 4.95-5.01 (m, 2H), 5.60-5.75 (m, 2H), 5.95 (s, 1H), 6.58 (d, 1H, *J* = 2.6), 6.73 (dd, 1H, *J* = 2.6, 8.5), 7.12 (d, 1H, *J* = 8.5).

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The title compound of this example was prepared by procedures analogous to those described above in Example 3.

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Example 176 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-(2-propenyl)-, (4a*S*-*trans*)-

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The title compound of this example was prepared by procedures analogous to those described above or below in Example 6. MS: 357 (M+1)⁺.

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Example 177 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[2-(4-morpholinyl)ethyl]-, (4a*S*,10a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 33. MS: 390 (M+1)⁺.

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Example 178 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(2-propenyl)-, [2*R*-(2α,4αα,10αα)]-

The title compound of this example was prepared by procedures analogous to those described above for the preparation of the title compound of Example 8. ¹H NMR (400 MHz, CD₃OD) δ 4.95-4.99 (m, 2H), 5.60-5.80 (m, 2H), 6.50 (d, 1H, J = 2.4), 6.57 (dd, 1H, J = 2.4, 8.5), 7.03 (d, 1H, J = 8.5).

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Examples 179-181

The title compounds of Examples 179-181 were prepared by procedures analogous to those described above in Example 33.

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Example 179 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[2-(4-hydroxy-1-piperidinyl)ethyl]-, [2*R*-(2α,4αα,10αβ)]-, MS: 404 (M+1)⁺.

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Example 180 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[2-(4-methyl-1-piperazinyl)ethyl]-, [2*R*-(2α,4αα,10αβ)]-, MS: 403 (M+1)⁺.

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Example 181 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[2-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]ethyl]-, [2*R*-(2α,4αα,10αβ)]-, MS: 477 (M).

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Example 182 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(2-hydroxy-2-phenylethyl)-, [2*R*-(2α,4αα,10αβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 136. MS: 396 (M).

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Example 183 2-Butenoic acid, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-, ethyl ester, [2*R*-(2 α ,4 $\alpha\alpha$ (*E*),10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 35. MS: 406 (M+18)⁺.

Example 184 4a(2*H*)-Phenanthreneacetaldehyde, 2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-, *O*-methyloxime, [2*R*-(2 α ,4 $\alpha\alpha$,10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 34. ¹H NMR (400 MHz, CD₃OD) δ 3.70 (s) and 3.74 (s, 3H).

Example 185 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-propyl-, (4a*R*-*cis*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 7. ¹H NMR (400 MHz, CD₃OD) δ 0.826 (t, 3H, J = 7). MS: 276 (M+18)⁺.

Example 186 2-Phenanthrenol, 4b,5,6,7,8,8a,9,10-octahydro-4b-propyl-7-propylidene-, [4b*R*-(4b α ,7*Z*,8 $\alpha\alpha$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 78. MS: 285 (M+1)⁺.

Example 187 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(2-propenyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 $\alpha\alpha$,10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 279 (M-17)⁺.

Examples 188-189

The title compounds of Examples 188-189 were prepared by procedures analogous to those described above in Example 7.

Example 188 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-propyl-, (4a*R*-*trans*)-, MS: 259 (M+1)⁺.

Example 189 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2,4a-dipropyl-, [2*R*-(2 α ,4 $\alpha\alpha$,10 $\alpha\beta$)]-, MS: 285 (M-17)⁺.

Example 190 Piperazine, 1-[4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-oxo-2-butenyl]-4-[2-(2-hydroxyethoxy)ethyl]-, [2*R*-(2 α ,4 α (*E*),10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 37. MS: 517 (M).

Example 191 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-, [2*S*-(2 α ,4 α β ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 7. MS: 243 (M-17)*.

Examples 192-193

The title compounds of Examples 192-193 were prepared by procedures analogous to those described above in Example 136.

Example 192 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2,4a-dipropyl-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 285 (M-17)*.

Example 193 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2,4a-dipropyl-, [2*S*-(2 α ,4 α β ,10 α β)]-, MS: 285 (M-17)*.

Example 194 Piperazine, 1-[4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-oxo-2-butenyl]-4-methyl-, [2*R*-(2 α ,4 α (*E*),10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 37. MS: 443 (M+1)*.

Example 195 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-(2-thienyl)-2-propenyl]-, [4a*S*(*E*)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 35. MS: 382 (M-18)*.

Example 196 2-Phenanthrenol, 4b,5,6,7,8,8a,9,10-octahydro-4b,7-dipropyl-, (4b*R*,8a*S*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 10. MS: 287 (M+1)*.

Examples 197-202

The title compounds of Examples 197-202 were prepared by procedures analogous to those described above in Example 37.

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Example 197 4-Piperidinol, 1-[4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-1-oxo-2-butenyl]-, [2*R*-[2 α ,4 α (*E*),10a β]]-, MS: 426 (M-17)⁺.

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Example 198 2-Butenamide, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-*N*-(3-(dimethylamino)propyl)-, [2*R*-[2 α ,4 α (*E*),10a β]]-, MS: 446 (M+1)⁺.

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Example 199 2-Butenamide, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-*N,N*-diethyl-, [2*R*-[2 α ,4 α (*E*),10a β]]-, MS: 416 (M+1)⁺.

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Example 200 2-Butenamide, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-*N*-(3-(4-morpholinyl)propyl)-, [2*R*-[2 α ,4 α (*E*),10a β]]-, MS: 487 (M).

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Example 201 2-Butenamide, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-*N*-(2-pyridinylmethyl)-, [2*R*-[2 α ,4 α (*E*),10a β]]-, MS: 452 (M+1)⁺.

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Example 202 2-Butenamide, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-*N*-(4-pyridinylmethyl)-, [2*R*-[2 α ,4 α (*E*),10a β]]-, MS: 451 (M+1)⁺.

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Example 203 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-(2-pyridinyl)-2-propenyl]-, [2*R*-[2 α ,4 α (*E*),10a β]]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 35. MS: 394 (M+1)⁺.

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Example 204 2-Butenamide, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-*N*-[2-(4-pyridinyl)ethyl]-, [2*R*-[2 α ,4 α (*E*),10a β]]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 37. MS: 465 (M+1)⁺.

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Example 205 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[3-(5-isoxazolyl)-2-propenyl]-, [4a*S*(*E*),10a*R*]-

The title compound of this example was prepared by procedures analogous to those described above in Example 35. MS: 366 (M-17)⁺.

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Example 206 2-Butenamide, 4-[2-(chloroethynyl)-1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-4a(2*H*)-phenanthrenyl]-*N*-ethyl-, [2*R*-[2α,4αα(*E*),10αβ]]-

The title compound of this example was prepared by procedures analogous to those described above in Example 37. MS: 370 (M-17)⁺.

Example 207 2-Phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(2-propenyl)-7-(1-propynyl)-, [4b*S*-(4bα,7α,8aβ)]-, ¹³C NMR (100 MHz, CDCl₃) δ 116.6, 168.5

The title compound of this example was prepared by procedures analogous to those described above in Example 9.

Examples 208-209

The title compounds of Examples 208-209 were prepared by procedures analogous to those described above in Example 8.

Example 208 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(3-phenylpropyl)-, (4a*R*)-, MS: 377 (M-17)⁺.

Example 209 2,7-Phenanthrenediol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(3-phenylpropyl)-, [2*S*-(2α,4aβ,10αα)]-, MS: 377 (M-17)⁺.

Examples 210-212

The title compounds of Examples 210-212 were prepared by procedures analogous to those described above in Example 18.

Example 210 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(2-propenyl)-7-(1-propynyl)-, [4b*S*-(4bα,7α,8aβ)]-, MS: 324 (M+1)⁺.

Example 211 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N,N*-dimethyl-4b-(2-propenyl)-7-(1-propynyl)-, [4b*S*-(4bα,7α,8aβ)]-, MS: 353 (M+1)⁺.

Example 212 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4bα,7α,8aβ)]-, MS: 374 (M+1)⁺.

Examples 213-214

The title compounds of Examples 213-214 were prepared by procedures analogous to those described above in Example 9.

Example 213 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 313 (M-17)*.

Example 214 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*S*-(2 α ,4 α ,10 α)]-, MS: 313 (M-17)*.

Examples 215-216

The title compounds of Examples 215-216 were prepared by procedures analogous to those described above in Example 10.

Example 215 2-Phenanthrenol, 7-fluoro-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, (4*aS*,10*aS*)-, MS: 352 (M).

Example 216 2-Phenanthrenol, 7-fluoro-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, (4*aS*,10*aS*)-, MS: 352 (M).

Example 217 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-methyl-4b-(phenylmethyl)-7-(1-propynyl)-, [4*bS*-(4*b* α ,7 α ,8 α)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 18. MS: 388 (M+1)*.

Examples 218-219

The title compounds of Examples 218-219 were prepared by procedures analogous to those described above in Example 9.

Example 218 2-Phenanthrenol, 7-fluoro-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*S*-(2 α ,4 α ,10 α)]-, MS: 331 (M-17)*.

Example 219 2-Phenanthrenol, 7-fluoro-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 331 (M-17)*.

Example 220 2-Phenanthrenecarboxamide, 4b-[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-, [4*bS*-(4*b* α ,7 α ,8 α)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 18. MS: 398 (M+1)*.

Example 221 2-Phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, methyl ester, [4bS-(4b α ,7 β ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 14. MS: 371 (M-17)*.

Example 222 2-Phenanthrenemethanol, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-a,a-dimethyl-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 19. MS: 371 (M-17)*.

Example 223 Carbamic acid, [4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]-, 2-(dimethylamino)ethyl ester, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 28. MS: 461 (M+1)*.

Example 224 2-Phenanthrenol, 7-(chloromethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2R-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 361 (M-17)*.

Examples 225-231

The title compounds of Examples 225-231 were prepared by procedures analogous to those described above in Example 18.

Example 225 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(3-phenyl-2-propenyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-, MS: 400 (M+1)*.

Example 226 2-Phenanthrenecarboxamide, N-[2-(dimethylamino)ethyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-, MS: 445 (M+1)*.

Example 227 2-Phenanthrenecarboxamide, N-[6-(dimethylamino)hexyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-, MS: 501 (M+1)*.

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Example 228 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-[2-(1-pyrrolidinyl)ethyl]-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 471 (M+1)⁺.

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Example 229 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[3-(4-methyl-1-piperazinyl)propyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 514 (M+1)⁺.

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Example 230 2-Phenanthrenecarboxamide, *N*-[3-(dimethylamino)propyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 459 (M+1)⁺.

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Example 231 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[2-(4-morpholinyl)ethyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 487 (M+1)⁺.

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Example 232 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[2-(4-morpholinyl)ethyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]- HCl salt

The title compound of this example is the HCl salt of the title compound of Example 231. MS: 487 (M+1)⁺.

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Examples 233-237

20 The title compounds of Examples 233-237 were prepared by procedures analogous to those described above in Example 18.

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Example 233 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 β ,8a β)]-, MS: 374 (M+1)⁺.

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Example 234 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[3-(1*H*-imidazol-1-yl)propyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt, MS: 483 (M+1)⁺.

Example 235 2-Phenanthrenecarboxamide, *N*-[4-(dimethylamino)butyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 473 (M+1)⁺.

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Example 236 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[3-(4-morpholinyl)propyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 501 (M+1)⁺.

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Example 237 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[3-(4-morpholinyl)propyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt, MS: 501 (M+1)⁺.

Example 238 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 281 (M-17)⁺.

Examples 239-240

The title compounds of Examples 239-240 were prepared by procedures analogous to those described above in Example 18.

Example 239 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-(3-methoxypropyl)-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 446 (M+1)⁺

Example 240 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[3-(2-methoxyethoxy)propyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 490 (M+1)⁺

Example 241 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-(4-pyridinylmethyl)-, [4b*S*-(4b α ,7 α ,8a β)]-

To a stirring solution of 779 mg of 4-aminomethylpyridine in 10 mL of dichloromethane at 0 °C under N₂ was added 3.6 mL of 2.0 M trimethylaluminum in toluene. The mixture was stirred at 0 °C for 20 min. then at RT for 1 h. To this mixture was added 350 mg of the title compound of Example 14 in 5 mL of dichloromethane. The mixture was heated to reflux overnight. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane to 10% MeOH in dichloromethane as the gradient eluant afforded 362 mg (87 %) of the title product of this example as a white solid. MS: 465 (M+1)⁺.

Example 242 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-(4-pyridinylmethyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, HCl salt

The title compound of this example is the HCl salt of the title compound of Example 241. MS: 465 (M+1)⁺.

Example 243 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-[2-(4-pyridinyl)ethyl]-, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 241. MS: 479 (M+1)⁺.

Example 244 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(2-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)]-

To a stirring solution of 6.2 g of 2-aminomethylpyridine in 80 mL of dichloromethane at 0 °C under N₂ was added 26 mL of 2.0 M trimethylaluminum in toluene. The mixture was stirred at 0 °C for 20 min. then at RT for 1 h. To this mixture was added 2.2 g of the title compound of Example 14 (which was made by procedures described in Example 14) in 50 mL of dichloromethane. The mixture was heated to reflux overnight. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane to 10% MeOH in dichloromethane as the gradient eluant afforded 1.4 g (53 %) of the title product of this example as a white solid. MS: 465 (M+1)⁺.

Examples 245-247

The compounds of Examples 245-247 were prepared by procedures analogous to those described above in Example 244.

Example 245 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(2-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 244. MS: 465 (M+1)⁺.

Example 246 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-[2-(2-pyridinyl)ethyl]-, [4bS-(4b α ,7 α ,8a β)]-, MS: 479 (M+1)⁺.

Example 247 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-[(tetrahydro-2-furanyl)methyl]-, [4bS-(4b α ,7 α ,8a β)]-, MS: 458 (M+1)⁺.

Example 248 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(3-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)]-

To a stirring solution of 0.21 mL of 3-aminomethylpyridine in 1 mL of dichloromethane at 0 °C under N₂ was added 0.1 mL of 2.0 M trimethylaluminum in hexane. The mixture was stirred at 0 °C for 20 min. then at RT for 1 h. To this mixture was added 20 mg of the title compound of Example 14 in 1 mL of dichloromethane. The mixture was heated to reflux overnight. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 5% MeOH in dichloromethane to 10% MeOH in dichloromethane as the gradient eluant afforded 18 mg (75 %) of the title product of this example as a white solid. MS: 465 (M+1)⁺.

Example 249 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(3-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)]-HCl-salt

The title product of this example is the HCl salt of the title product of Example 248. MS: 465 (M+1)⁺

Example 250 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[2-(1-methyl-2-pyrrolidinyl)ethyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 248. MS: 485 (M+1)⁺.

Example 251 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[2-(1-methyl-2-pyrrolidinyl)ethyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 251. MS: 485 (M+1)⁺.

Examples 252-253

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The title compounds of Examples 252-253 were prepared by procedures analogous to those described above in Example 9.

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Example 252 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 309 (M-17)*.

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Example 253 2,7-Phenanthrenediol, 4a-butyl-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 295 (M-17)*.

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Example 254 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-[3-(1-pyrrolidinyl)propyl]-, [4*bS*-(4 $\beta\alpha$,7 α ,8 $\alpha\beta$)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 248. MS: 485 (M+1)*.

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Example 255 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-[3-(1-pyrrolidinyl)propyl]-, [4*bS*-(4 $\beta\alpha$,7 α ,8 $\alpha\beta$)]-HCl salt

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The title product of this example is the HCl salt of the title product of Example 254. MS: 485 (M+1)*.

Example 256 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-[3-(1*H*-1,2,4-triazol-1-yl)propyl]-, [4*bS*-(4 $\beta\alpha$,7 α ,8 $\alpha\beta$)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 248. MS: 483 (M+1)*.

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Example 257 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-[3-(1*H*-1,2,4-triazol-1-yl)propyl]-, [4*bS*-(4 $\beta\alpha$,7 α ,8 $\alpha\beta$)]-HCl salt

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The title product of this example is the HCl salt of the title product of Example 256. MS: 483 (M+1)*.

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Example 258 2,7-Phenanthrenediol, 4a-(3-butenyl)-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 293 (M-17)*.

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Example 259 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[5-(4-morpholinyl)pentyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4*bS*-(4 $\beta\alpha$,7 α ,8 $\alpha\beta$)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 248. MS: 529 (M+1)⁺.

Example 260 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[5-(4-morpholinyl)pentyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]- HCl salt

The title compound of this example is the HCl salt of the title compound of Example 259. MS: 529 (M+1)⁺.

Example 261 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-pentyl-7-(1-propynyl)-*N*-[3-(1*H*-1,2,4-triazol-1-yl)propyl]-, [4b*R*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 248. MS: 463 (M+1)⁺.

Example 262 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-pentyl-7-(1-propynyl)-*N*-[3-(1*H*-1,2,4-triazol-1-yl)propyl]-, [4b*R*-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 261. MS: 463 (M+1)⁺.

Examples 263-265

The title compounds of Examples 263-265 were prepared by procedures analogous to those described above for the preparation of the title compound of Example 59.

Example 263 Carbamic acid, dimethyl-, 7-(chloroethynyl)-4b,5,6,7,8,8a,9,10-octahydro-7-methoxy-4b-(2-methoxyethyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 420 (M+1)⁺.

Example 264 Carbamic acid, dimethyl-, 7-(chloroethynyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(2-methoxyethyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 406 (M+1)⁺.

Example 265 Carbamic acid, dimethyl-, 7-(chloroethynyl)-4b-[2-[2-(dimethylamino)-2-oxoethoxy]ethyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, ¹H NMR (400 MHz, CDCl₃) δ 2.94 (s, 3H), 2.96 (s, 3H), 3.06 (s, 3H), 3.09 (s, 3H), 4.34 (s, 2H).

Example 266-267

The title compounds of Examples 266-267 were prepared by procedures analogous to those described above in Example 248.

Example 266 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-2-pyridinyl-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 451 (M+1)⁺.

Example 267 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-2-pyridinyl-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt, MS: 451 (M+1)⁺.

Example 268 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-pyrazinyl-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. MS: 452 (M+1)⁺.

Examples 269-270

The title products of Examples 269-270 are the HCl salt and the *p*-methanesulfonic acid salt, respectively, of the title product of Example 268.

Example 269 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-pyrazinyl-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt, MS: 452 (M+1)⁺.

Example 270 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-pyrazinyl-, [4b*S*-(4b α ,7 α ,8a β)]-*p*-methanesulfonic acid salt, MS: 452 (M+1)⁺.

Example 271 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-3-pyridinyl-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 248. MS: 450 (M).

Example 272 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-3-pyridinyl-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 271. MS: 451 (M+1)⁺.

Examples 273-274

The title compounds of Examples 273-274 were prepared by procedures analogous to those described above in Example 248.

Example 273 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-4-pyrimidinyl-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 452 (M+1)⁺.

Example 274 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-propyl-7-(1-propynyl)-*N*-(4-pyridinylmethyl)-, [4b*R*-(4b α ,7 α ,8a β)]-, MS: 417 (M+1)⁺.

Example 275 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-propyl-7-(1-propynyl)-*N*-(4-pyridinylmethyl)-, [4b*R*-(4b α ,7 α ,8a β)]- HCl salt

The title compound of this example is the HCl salt of the title compound of Example 274. MS: 417 (M+1)⁺.

Example 276 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-1,3,4-thiadiazol-2-yl-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 248. MS: 458 (M+1)⁺.

Example 277 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-1,3,4-thiadiazol-2-yl-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 276. MS: 458 (M+1)⁺.

Example 278 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-2-pyrimidinyl-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 248. MS: 452 (M+1)⁺.

Example 279 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-2-pyrimidinyl-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 278. MS: 452 (M+1)⁺.

Examples 280-283

The title compounds of Examples 280-283 were prepared by procedures analogous to those described above in Example 248.

Example 280 2-Phenanthrenecarboxamide, *N*-(cyanomethyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 413 (M+1)⁺.

Example 281 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-(1*H*-tetrazol-5-ylmethyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 454 (M-1)⁺.

Example 282 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-1,2,4-triazin-3-yl-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 453 (M+1)⁺.

Example 283 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-methoxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-pyrazinyl-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 466 (M+1)⁺.

Example 284 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-methoxy-4b-(phenylmethyl)-7-(1-propynyl)-*N*-pyrazinyl-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 283. MS: 466 (M+1)⁺.

Example 285 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-7-(2-thiazolyl)-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 16. MS: 366 (M+1)⁺.

Examples 286-287

The title compounds of Examples 286-287 were prepared by procedures analogous to those described above in Example 248.

Example 286 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-(5-methyl-1*H*-pyrazol-3-yl)-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 454 (M+1)⁺.

Example 287 1*H*-Pyrazol-3-amine, 5-methyl-1-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-

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phenanthrenyl]carbonyl]-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 454 (M+1)⁺.

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Example 288 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-7-(3-pyridinyl)-, [2*R*-(2 α ,4 α ,10a β)]-

5 The title compound of this example was prepared by procedures analogous to those described above in Example 16. MS: 360 (M+1)⁺.

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Example 289 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-7-(3-pyridinyl)-, [2*R*-(2 α ,4 α ,10a β)]-HCl salt

10 The title product of this example is the HCl salt of the title product of Example 288. MS: 360 (M+1)⁺.

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Example 290 Carbamic acid, [2-(4-morpholinyl)ethyl]-, 4b-butyl-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-

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15 The title compound of this example was prepared by procedures analogous to those described above in Example 59. MS: 469 (M+1)⁺.

Example 291 Carbamic acid, [2-(4-morpholinyl)ethyl]-, 4b-butyl-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-HCl salt

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20 The title product of this example is the HCl salt of the title product of Example 290. MS: 469 (M+1)⁺.

Example 292 Carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b-butyl-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-

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25 The title compound of this example was prepared by procedures analogous to those described above in Example 59. MS: 453 (M+1)⁺.

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Example 293 2(3*H*)-Phenanthrenone, 7-fluoro-4,4a,9,10-tetrahydro-4a-(phenylmethyl)-, (*S*)-, ¹H NMR (400 MHz, CDCl₃) δ 5.99 (s, 1H), 6.88-6.93 (m, 1H).

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30 The title compound of this example was prepared by procedures analogous to those described above in Example 1.

Example 294 Carbamic acid, [2-(dimethylamino)ethyl]-, 4b-butyl-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 59. MS: 427 (M+1)⁺.

Examples 295-296

The title compounds of Examples 295-296 were prepared by procedures analogous to those described above in Example 16.

Example 295 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-(5-methyl-1*H*-1,2,4-triazol-3-yl)-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2α,4α,10aβ)]- and 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-(5-methyl-1*H*-1,2,4-triazol-3-yl)-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-, MS: 413 (M+2)⁺

Example 296 2-Phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-propyl-7-(1-propynyl)-, [4b*R*-(4bα,7α,8aβ)]-, MS: 290 (M-17)⁺.

Example 297 2-Phenanthrenol, 4a-butyl-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-7-(pyrazinyloxy)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. MS: 391 (M+1)⁺.

Examples 298-299

The title compounds of Examples 298-299 were prepared by procedures analogous to those described above in Example 16.

Example 298 2-Phenanthrenol, 4a-butyl-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-7-(2-thiazolyl)-, [2*R*-(2α,4α,10aβ)]-, MS: 380 (M+1)⁺.

Example 299 2-Phenanthrenol, 4a-butyl-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-7-(2-pyridinyl)-, [2*R*-(2α,4α,10aβ)]-, MS: 3374 (M+1)⁺.

Example 300 2-Phenanthrenol, 4a-butyl-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-7-(2-pyridinyl)-, [2*R*-(2α,4α,10aβ)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 299. MS: 3374 (M+1)⁺.

Example 301 2-Phenanthrenol, 4a-butyl-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-7-(2-pyrimidinylloxy)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. MS: 391 (M+1)⁺.

Example 302 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-thiazolyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 16. MS: 414 (M+1)⁺.

Example 303 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-pyridinyl)-, [2*R*-(2α,4α,10aβ)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 16. MS: 408 (M+1)⁺.

Example 304 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(3-pyridinyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 16. MS: 408 (M+1)⁺.

Example 305 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(3-pyridinyl)-, [2*R*-(2α,4α,10aβ)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 304. MS: 408 (M+1)⁺.

Example 306 2-Phenanthrenol, 4a-butyl-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-7-(pyrazinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 405 (M+1)⁺.

Example 307 2-Phenanthrenol, 4a-butyl-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-7-(pyrazinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 306. MS: 405 (M+1)⁺.

Example 308 4*H*-Benzo[a]quinolizin-4-one, 1,2,3,6,7,11b-hexahydro-9-hydroxy-11b-(phenylmethyl)-3-propyl-

The title compound of this example was prepared by procedures analogous to those described above in Example 40. MS: 350 (M+1)⁺.

Examples 309-311

The title compounds of Examples 309-311 were prepared by procedures analogous to those described above in Example 15.

Example 309 2-Phenanthrenecarbonitrile, 4b-butyl-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-, [4b*R*-(4b α ,7 α ,8a β)]-, MS: 322 (M+1)⁺.

Example 310 2-Phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-(2-propenyloxy)-4b-propyl-7-(1-propynyl)-, [4b*R*-(4b α ,7 α ,8a β)]-, ¹H NMR (400 MHz, CD₃OD) δ 5.88-5.97 (m, 1H)

Example 311 Acetic acid, [[7-cyano-1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-2-phenanthrenyl]oxy]-, ethyl ester, [2*R*-(2 α ,4 α ,10a β)]-, ¹H NMR (400 MHz, CD₃OD) δ 4.25 (s, 1H).

Example 312 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(4-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound was obtained as described in Example 627, below, except 4-picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.

Mass: 442 (M+1)⁺

Example 313 2-Phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-, [4b*S*-(4b α ,7 α ,8a β)]-, ¹H NMR (400 MHz, CD₃OD) δ 0.88 (t, 3H, J = 7.3), 6.43 (d, 1H, J = 8.3)

The title compound of this example was prepared by procedures analogous to those described above in Example 15.

Example 314 2-Phenanthrenol, 7-(5-hexenyloxy)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 63. MS: 415 (M-17)⁺.

Example 315 2-Phenanthrenol, 7-[(4-ethenylphenyl)methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, (4a*S*,10a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 39. MS: 449 (M-17)⁺.

Example 316 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-(6-methyl-2-pyridinyl)-4b-(phenylmethyl)-7-propyl-, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. MS: 469 (M+1)⁺.

Example 317 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-(6-methyl-2-pyridinyl)-4b-(phenylmethyl)-7-propyl-, [4bS-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 316. MS: 534 (M+1)⁺.

Example 318 2-Phenanthrenol, 7-[[5-(2,6-dimethyl-4-morpholinyl)pentyl]oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2R-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 12. MS: 469 (M+1)⁺.

Examples 319-320

The title compounds of Examples 319-320 were prepared by procedures analogous to those described above in Example 136.

Example 319 2,7-Phenanthrenediol, 2-(4-fluorophenyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, (4aS,10aR)-, MS: 385 (M-17)⁺.

Example 320 2,7-Phenanthrenediol, 2-(4-fluorophenyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, (4aS,10aR)-, MS: 385 (M-17)⁺.

Example 321 2-Phenanthrenol, 4b,5,6,7,8,8a,9,10-octahydro-7-phenyl-4b-(phenylmethyl)-, (4bS,8aR)-, ¹H NMR (400 MHz, CDCl₃) δ 6.58-6.63 (m 2H)

The title compound of this example was prepared by procedures analogous to those described above in Example 10.

Examples 322-323

The title compounds of Examples 322-323 were prepared by procedures analogous to those described above in Example 12.

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Example 322 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-[[5-(1-piperidinyl)pentyl]oxy]-2-propyl-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 504 (M+1)⁺.

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Example 323 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-[[5-(1-pyrrolidinyl)pentyl]oxy]-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 490 (M+1)⁺.

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Example 324 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(6-methyl-2-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4*bS*-(4*b* α ,7 α ,8 $\alpha\beta$)]-

10 The title compound of this example was prepared by procedures analogous to those described below in Example 332. MS: 483 (M-17)⁺.

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Example 325 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(6-methyl-2-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4*bS*-(4*b* α ,7 α ,8 $\alpha\beta$)]- HCl salt

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15 The title compound of this example is the HCl salt of the title compound of Example 324. MS: 483 (M-17)⁺.

Example 326 2-Phenanthrenecarboxamide, 7-(4,6-dimethyl-2-pyridinyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-, [4*bS*-(4*b* α ,7 α ,8 $\alpha\beta$)]-

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20 The title compound of this example was prepared by procedures analogous to those described below in Example 332. MS: 483 (M-17)⁺.

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Example 327 2-Phenanthrenecarboxamide, *N*-(4,6-dimethyl-2-pyridinyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-, [4*bS*-(4*b* α ,7 α ,8 $\alpha\beta$)]- HCl salt

25 The title compound of this example is the HCl salt of the title compound of Example 326. MS: 483 (M-17)⁺.

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Examples 328-331

The title compounds of Examples 328-331 were prepared by procedures analogous to those described below in Example 332.

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30 Example 328 2-Phenanthrenecarboxamide, 7-(4,6-dimethyl-2-pyridinyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4*bS*-(4*b* α ,7 α ,8 $\alpha\beta$)]-, MS: 479 (M+1)⁺.

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Example 329 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-(6-methyl-2-pyridinyl)-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)], MS: 465 (M+1)⁺.

Example 330 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(6-methyl-2-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)], MS: 479 (M+1)⁺.

Example 331 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(6-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)], MS: 479 (M+1)⁺.

Example 332 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)].

To a stirring solution of 250 mg of 2-methyl-3-aminomethylpyridine in 5 mL of dichloromethane at 0 °C under N₂ was added 1.02 mL of 2.0 M trimethylaluminum in toluene. The mixture was stirred at 0 °C for 20 min. then at RT for 1 h. To this mixture was added 100 mg of the title compound of Example 14 in 5 mL of dichloromethane. The mixture was heated to reflux overnight. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 90% EtOAc in hexanes as the eluant afforded 99 mg (80 %) of the title product of this example as a white solid. MS: 479 (M+1)⁺.

Examples 333-336

The compounds of Examples 333-336 were prepared by procedures analogous to those described above in Example 244.

Example 333 2-Phenanthrenecarboxamide, N-(4,6-dimethyl-2-pyrimidinyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)], MS: 480 (M+1)⁺.

Example 334 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-(4-methyl-2-pyrimidinyl)-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)], MS: 466 (M+1)⁺.

Example 335 2-Phenanthrenecarboxamide, *N*-(2,6-dimethyl-4-pyrimidinyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)], MS: 480 (M+1)⁺.

Example 336 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propenyl)-, [2*R*]-[2 α ,2(*E*),4 α ,10a β]], MS: 347 (M-1)⁺.

Example 337 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 332. MS: 479 (M+1)⁺.

Example 338 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4b*S*-(4b α ,7 α ,8a β)]-

To a stirring solution of 232 mg of 2-methyl-3-aminomethylpyridine in 10 mL of dichloromethane at 0 °C under N₂ was added 0.95 mL of 2.0 M trimethylaluminum in toluene. The mixture was stirred at 0 °C for 20 min. then at RT for 1 h. To this mixture was added 300 mg of 2-phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propyl)-, methyl ester, [4b*S*-(4b α ,7 α ,8a β)]- in 10 mL of dichloromethane. The mixture was heated to reflux overnight. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 10 % isopropanol and 1 % acetone in hexanes to 30 % isopropanol and 5 % acetone in hexanes as the gradient eluant afforded 303 mg (80 %) of the title product of this example as a white solid. ¹H NMR (400 MHz, CDCl₃) δ 2.56 (s, 2H), MS: 483 (M+1)⁺.

Example 339 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 338. ¹H NMR (400 MHz, CD₃OD) δ 2.56 (s, 2H), MS: 483 (M+1)⁺.

Examples 340-342

The title compounds of Examples 340-342 were prepared by procedures analogous to those described above in Example 338.

Example 340 2-Phenanthrenecarboxamide, *N*-[(2-chloro-6-methyl-4-pyridinyl)methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 517 (M).

Example 341 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-4-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 483 (M+1)⁺.

Example 342 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-(2-pyridinylmethyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 469 (M+1)⁺.

Example 343 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-(2-pyridinylmethyl)-, [4b*S*-(4b α ,7 α ,8a β)]-HCl salt

The title product of this example is the HCl salt of the title product of Example 342. MS: 469 (M+1)⁺.

Examples 344-345

The title compounds of Examples 344-345 were prepared by procedures analogous to those described above in Example 338.

Example 344 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-(4-pyridinylmethyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 469 (M+1)⁺.

Example 345 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-(3-pyridinylmethyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 469 (M+1)⁺.

Examples 346-347

The title compounds of Examples 346-347 were prepared by procedures analogous to those described above in Example 9.

Example 346 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(4-methyl-1-pentynyl)-4a-(phenylmethyl)-, [2*R*-(2 α ,4a α ,10a β)]-, MS: 371 (M-17)⁺.

Example 347 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methyl-1-butyryl)-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-, MS: 357 (M-17)⁺.

Example 348 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(3,3,3-trifluoropropyl)-, [2*S*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 10. MS: 487 (M-17)⁺.

Examples 349-350

The title compounds of Examples 349-350 were prepared by procedures analogous to those described above in Example 338.

Example 349 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-pyrazinyl-, [4b*S*-(4bα,7α,8aβ)]-, MS: 456 (M+1)⁺.

Example 350 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-2-pyridinyl-, [4b*S*-(4bα,7α,8aβ)]-, ¹H NMR (400 MHz, CD₃OD) δ 7.22 (d, 1H, J = 1).

Examples 351-353

The title compounds of Examples 351-353 were prepared by procedures analogous to those described above in Example 10.

Example 351 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(2-methylpropyl)-4a-(phenylmethyl)-, [2*R*-(2α,4aβ,10aα)]-, MS: 347 (M-17)⁺.

Example 352 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(2-methylpropyl)-4a-(phenylmethyl)-, [2*R*-(2α,4aα,10aβ)]-, MS: 347 (M-17)⁺.

Example 353 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methylbutyl)-4a-(phenylmethyl)-, [2*R*-(2α,4aα,10aβ)]-, MS: 361 (M-17)⁺.

Examples 354-355

The title compounds of Examples 354-355 were prepared by procedures analogous to those described above in Example 74.

Example 354 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methyl-1-butynyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 448 (M-17)⁺.

Example 355 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-(3,3,3-trifluoropropyl)-, [2*S*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 496 (M+1)⁺.

Example 356 4*H*-Benzo[a]quinolizin-4-one, 1,2,3,6,7,11b-hexahydro-9-hydroxy-3-(hydroxymethyl)-11b-(phenylmethyl)-3-propyl-, (3*S*-*cis*)-, ¹H NMR (400 MHz, CD₃OD) δ 4.53 (dm, 1H, J = 13).

The title compound of this example was prepared by procedures analogous to those described above in Example 42.

Examples 357-358

The title compounds of Examples 357-358 were prepared by procedures analogous to those described above in Example 9.

Example 357 2-Phenanthreneacetonitrile, 1,2,3,4,4a,9,10,10a-octahydro-2,7-dihydroxy-4a-(phenylmethyl)-, (4*aS*,10*aR*)-, MS: 346 (M-1)⁺

Example 358 2-Phenanthreneacetonitrile, 1,2,3,4,4a,9,10,10a-octahydro-2,7-dihydroxy-4a-(phenylmethyl)-, (4*aS*,10*aR*)-, MS: 346 (M-1)⁺.

Examples 359-360

The title compounds of Examples 359-360 were prepared by procedures analogous to those described above in Example 136.

Example 359 2,7-Phenanthrenediol, 2-cyclopentyl-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, (4*aS*,10*aR*)-, MS: 359 (M-17)⁺.

Example 360 2,7-Phenanthrenediol, 2-cyclohexyl-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, (4*aS*,10*aR*)-, MS: 389 (M-1)⁺.

Examples 361-363

The title compounds of Examples 361-363 were prepared by procedures analogous to those described above in Example 332.

Example 361 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-4-pyridinyl-, [4*bS*-(4*b* α ,7*a* α ,8*a* β)]-, MS: 455 (M+1)⁺.

- Example 362 2-Phenanthrenecarboxamide, *N*-(2,6-dichloro-4-pyridinyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 523 (M).
- Example 363 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-3-pyridinyl-, [4b*S*-(4b α ,7 α ,8a β)]-, MS: 455 (M+1)*.

Examples 364-365

The title compounds of Examples 364-365 were prepared by procedures analogous to those described above in Example 76.

- Example 364 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(2-methylpropyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*S*-(2 α ,4a α ,10a β)]-, MS: 456 (M+1)*.
- Example 365 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methylbutyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4a α ,10a β)]-, MS: 370 (M+1)*.

Examples 366-368

The title compounds of Examples 366-368 were prepared by procedures analogous to those described above in Example 10.

- Example 366 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(4-methylpentyl)-4a-(phenylmethyl)-, [2*R*-(2 α ,4a α ,10a β)]-, MS: 391 (M-1)*.
- Example 367 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(4-methylpentyl)-4a-(phenylmethyl)-, [2*S*-(2 α ,4a β ,10a α)]-, MS: 391 (M-1)*.
- Example 368 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-hydroxy-3-methylbutyl)-4a-(phenylmethyl)-, [2*S*-(2 α ,4a α ,10a β)]-, MS: 393 (M-1)*.

Examples 369-370

The title compounds of Examples 369-370 were prepared by procedures analogous to those described above in Example 76.

- Example 369 2-Phenanthrenepropanol, 1,2,3,4,4a,9,10,10a-octahydro-2-hydroxy- α,α -dimethyl-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*S*-(2 α ,4a α ,10a β)]-, MS: 486 (M+1)*.

Example 370 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(4-methylpentyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 484 (M+1)⁺.

Examples 371-372

5 The title compounds of Examples 371-372 were prepared by procedures analogous to those described above in Example 9.

Example 371 2,7-Phenanthrenediol, 2-(cyclopropylmethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*S*-(2 α ,4 α ,10 α)]-, MS: 363 (M+1)⁺.

10 Example 372 2,7-Phenanthrenediol, 2-(cyclopropylmethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 363 (M+1)⁺.

Example 373 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-hydroxypropyl)-4a-(phenylmethyl)-, (4*aS*,10*aR*)-

15 The title compound of this example was prepared by procedures analogous to those described above in Example 10. MS: 365 (M-1)⁺.

Examples 374-375

The title compounds of Examples 374-375 were prepared by procedures analogous to those described above in Example 9.

20 Example 374 2,7-Phenanthrenediol, 2-(3,3-dimethyl-1-butyryl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 387 (M-1)⁺.

Example 375 2,7-Phenanthrenediol, 2-(3,3-dimethyl-1-butyryl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*S*-(2 α ,4 α ,10 α)]-, MS: 387 (M-1)⁺.

25 Example 376 2-Phenanthrenol, 2-(cyclopropylethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-

30 The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 464 (M+1)⁺.

Example 377 2,7-Phenanthrenediol, 2-(2-cyclopropylethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 10. MS: 361 (M-17)*.

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Examples 378-379

The title compounds of Examples 378-379 were prepared by procedures analogous to those described above in Example 76.

- Example 378 2-Phenanthrenol, 2-(3,3-dimethyl-1-butynyl)-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-, ¹H NMR (400 MHz, CD₃OD) δ 8.61 (s, 1H).
- Example 379 2-Phenanthrenepropanol, 1,2,3,4,4a,9,10,10a-octahydro-2-hydroxy-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*S*-(2 α ,4 α ,10 α)]-, MS: 458 (M+1)*.

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Examples 380-381

The title compounds of Examples 380-381 were prepared by procedures analogous to those described above in Example 9.

- Example 380 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(phenylethynyl)-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 407 (M-1)*.
- Example 381 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(phenylethynyl)-4a-(phenylmethyl)-, [2*S*-(2 α ,4 α ,10 α)]-, MS: 407 (M-1)*.
- Example 382 2,7-Phenanthrenediol, 2-(3,3-dimethylbutyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 10. MS: 391 (M-1)*.

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- Example 383 2-Phenanthrenol, 2-(2-cyclopropylethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 450 (M-17)*.

- Example 384 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, (5)-

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5 The title compound of this example was prepared by procedures analogous to those described above in Example 3. Mass: 321 (M+1)⁺.

10 Example 385 (3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-4a-[(4-hydroxyphenyl)methyl]-7-methoxy-, (S)-

5 The title compound of this example was prepared by procedures analogous to those described above in Example 1. Mass: 335 (M+1)⁺.

15 Examples 386-387

The title compounds of Examples 386-387 were prepared by procedures analogous to those described above in Example 6.

10 Example 386 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, (4a*S*)-, Mass: 321 (M-1)⁺.

20 Example 387 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-4a-[(4-hydroxyphenyl)methyl]-7-methoxy-, (4a*S*)-, Mass: 335 (M-1)⁺.

25 Example 388 2,7-Phenanthrenediol, 2-(chloroethynyl)-2,3,4,4a,9,10-hexahydro-4a-[(4-hydroxyphenyl)methyl]-, (2*R*-*cis*)-

15 The title compound of this example was prepared by procedures analogous to those described above in Example 8. Mass: 363 (M-17)⁺.

30 Example 389 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-, (4a*S*)-

20 The title compound of this example was prepared by procedures analogous to those described above in Example 6. Mass: 325 (M+1)⁺.

Examples 390-391

35 The title compounds of Examples 390-391 were prepared by procedures analogous to those described above in Example 8.

25 Example 390 2-Phenanthrenol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-7-methoxy-, Mass: 397 (M+1)⁺.

40 Example 391 2-Phenanthrenol, 2-(chloroethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-7-methoxy-, Mass: 397 (M+1)⁺.

45 Examples 392-393

The title compounds of Examples 392-393 were prepared by procedures analogous to those described above in Example 10.

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Example 387

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Example 391

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Example 392 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-2-propyl-, (4a*S*)-, Mass: 366 (M), 384 (M+18)⁺.

Example 393 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-2-propyl-, (4a*S*)-, Mass: 366 (M), 384 (M+18)⁺.

Examples 394-406

The title compounds of Examples 394-406 were prepared by procedures analogous to those described above in Example 77.

Example 394 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-(phenylmethyl)-,oxime, (4a*S*)-, Mass: 322 (M+1)⁺.

Example 395 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-(phenylmethyl)-, *O*-(phenylmethyl)oxime, (4a*S*)-, Mass: 412 (M+1)⁺.

Example 396 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-(phenylmethyl)-, *O*-[(4-nitrophenyl)methyl]oxime, (4a*S*)-, Mass: 457 (M+1)⁺.

Example 397 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, *O*-ethyloxime, (*S*)-, Mass: 364 (M+1)⁺.

Example 398 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-1,7,10a-trihydroxy-4a-[(4-hydroxyphenyl)methyl]-, *O*-ethyloxime, Mass: 398 (M+1)⁺.

Example 399 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-1,7,10a-trihydroxy-4a-[(4-hydroxyphenyl)methyl]-, *O*-ethyloxime, Mass: 398 (M+1)⁺.

Example 400 Benzoic acid, [3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-2(1*H*)-phenanthrenylidene]hydrazide, (4a*S-trans*)-, Mass: 441 (M+1)⁺.

Example 401 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, *O*-2-propenyloxime, (4a*S-trans*)-, Mass: 378 (M+1)⁺.

Example 402 Acetic acid, [[[3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-2(1*H*)-phenanthrenylidene]amino]oxy]-, (4a*S-trans*)-, Mass: 396 (M+1)⁺.

Example 403 Hydrazinecarboxylic acid, [3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-2(1*H*)-phenanthrenylidene]-, ethyl ester, (4a*S-trans*)-, Mass: 409 (M+1)⁺.

Example 404 Acetic acid, [[[3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-2(1*H*)-phenanthrenylidene]amino]oxy]-, methyl ester, (4a*S-trans*)-, Mass: 410 (M+1)⁺.

Example 405 2(3*H*)-Phenanthrenone, 4,4a,9,10-tetrahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, *O*-methyloxime, Mass: 350 (M+1)⁺.

Example 406 3-Pyridinecarboxylic acid, [3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-2(1*H*)-phenanthrenylidene]hydrazide, (4a*S-trans*)-, Mass: 442 (M+1)⁺.

Example 407 Acetic acid, [4,4a,9,10-tetrahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-2(3*H*)-phenanthrenylidene]-, ethyl ester, [*S-(E)*]-

The title compound of this example was prepared by procedures analogous to those described above in Example 78. Mass: 391 (M+1)⁺.

Example 408 Acetic acid, cyano-, [3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-2(1*H*)-phenanthrenylidene]hydrazide, (4a*S-trans*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 77. Mass: 404 (M+1)⁺.

Example 409 2,7-Phenanthrenediol, 4a-[(4-aminophenyl)methyl]-1,2,3,4,4a,9,10,10a-octahydro-[2*R*-(2α,4α,10αβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 6. Mass: 322 (M-1)⁺.

Examples 410-411

The title compounds of Examples 410-411 were prepared by procedures analogous to those described above in Example 77.

Example 410 Hydrazinecarboxylic acid, [4,4a,9,10-tetrahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-2(3*H*)-phenanthrenylidene]-, ethyl ester, (*S*)-, Mass: 407 (M+1)⁺.

Example 411 2(1*H*)-Phenanthrenone, 4a-[(4-aminophenyl)methyl]-
3,4,4a,9,10,10a-hexahydro-7-hydroxy-, *O*-ethyloxime, Mass:
365 (M+1)*.

Examples 412-413

The title compounds of Examples 412-413 were prepared by procedures
analogous to those described above in Example 10.

Example 412 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-
[(1-methylethyl)amino]phenyl]methyl]-2-propyl-, (4a*S*,10a*R*)-,
Mass: 408 (M+1)*.

Example 413 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-
[(1-methylethyl)amino]phenyl]methyl]-2-propyl-, (4a*S*,10a*R*)-,
Mass: 408 (M+1)*.

Examples 414-415

The title compounds of Examples 414-415 were prepared by procedures
analogous to those described above in Example 77.

Example 414 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-
4a-[[4-[(1-methylethyl)amino]phenyl]methyl]-, *O*-ethyloxime,
(4a*S-trans*)-, Mass: 407 (M+1)*.

Example 415 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-
4a-[[4-[(1-methylethyl)amino]phenyl]methyl]-, *O*-methyloxime,
(4a*S-trans*)-, Mass: 393 (M+1)*.

Examples 416-418

The title compounds of Examples 416-418 were prepared by procedures
analogous to those described above in Example 78.

Example 416 2-Phenanthrenol, 4b,5,6,7,8,8a,9,10-octahydro-4b-[(4-
hydroxyphenyl)methyl]-7-propylidene-, (4b*S*,7*Z*)-, Mass: 349
(M+1)*.

Example 417 2-Phenanthrenol, 7-butyldiene-4b,5,6,7,8,8a,9,10-octahydro-
4b-[(4-hydroxyphenyl)methyl]-, (4b*S*,7*Z*)-, Mass: 363 (M+1)*.

Example 418 Acetonitrile, [3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-
hydroxyphenyl)methyl]-2(1*H*)-phenanthrenylidene]-, [4a*S*-
(2*Z*,4*α*,10*αβ*)]-, Mass: 363 (M+18)*.

Examples 419-421

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The title compounds of Examples 419-421 were prepared by procedures analogous to those described above in Example 136.

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Example 419 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-
5 [(tetrahydro-2H-pyran-4-yl)amino]phenyl]methyl]-2-propyl-,
(4aS,10aR)-, Mass: 450 (M+1)⁺.

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Example 420 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-
[(tetrahydro-2H-pyran-4-yl)amino]phenyl]methyl]-2-propyl-,
(4aS,10aR)-, Mass: 450 (M+1)⁺.

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Example 421 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-
10 [(1-methylethyl)amino]phenyl]methyl]-2-propyl-, (4aS,10aR)-,
Mass: 409 (M+1)⁺.

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Example 422 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-
hydroxyphenyl)methyl]-2-(1-hydroxypropyl)-, (4aS)-

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15 The title compound of this example was prepared by procedures analogous to
those described above in Example 30. Mass: 400 (M+18)⁺.

Examples 423-426

The title compounds of Examples 423-426 were prepared by procedures
analogous to those described above in Example 136.

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20 Example 423 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-
hydroxyphenyl)methyl]-2-propyl-, (4aS,10aR)-, Mass: 349
(M+17)⁺.

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Example 424 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-
hydroxyphenyl)methyl]-2-propyl-, (4aS,10aR)-, Mass: 349
(M+17)⁺.

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Example 425 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-
40 [[1-(1-methylethyl)-4-piperidinyl]amino]phenyl]methyl]-2-propyl-
, (4aS,10aR)-, Mass: 491 (M+1)⁺.

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Example 426 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[3-
30 [(1-methylethyl)amino]phenyl]methyl]-2-propyl-, (4aS,10aR)-,
Mass: 408 (M+1)⁺.

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Example 427 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-
hydroxyphenyl)methyl]-2-(1-hydroxypropyl)-, (4aS,10aS)-

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The title compound of this example was prepared by procedures analogous to
those described above in Example 30. Mass: 382 (M).

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Examples 428-429

The title compounds of Examples 428-429 were prepared by procedures analogous to those described above in Example 78.

Example 428 2-Phenanthrenol, 7-butyldiene-4b,5,6,7,8,8a,9,10-octahydro-4b-[(4-hydroxyphenyl)methyl]-, [4bS-(4b α ,7Z,8a α)]-, Mass: 363 (M+1)⁺.

Example 429 2-Phenanthrenol, 4b,5,6,7,8,8a,9,10-octahydro-4b-[(4-hydroxyphenyl)methyl]-7-pentyldiene-, [4bS-(4b α ,7Z,8a α)]-, Mass: 377 (M+1)⁺.

Examples 430-432

The title compounds of Examples 430-432 were prepared by procedures analogous to those described above in Example 77.

Example 430 2(1H)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, O-(phenylmethyl)oxime, (4aS-cis)-, Mass: 428 (M+1)⁺.

Example 431 2(1H)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, O-2-propenyloxime, (4aS-cis)-, Mass: 378 (M+1)⁺.

Example 432 2(1H)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-[(4-hydroxyphenyl)methyl]-, O-ethyloxime, (4aS-cis)-, Mass: 366 (M+1)⁺.

Example 433 2,7-Phenanthrenediol, 4a-[(3-aminophenyl)methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-propyl-, (4aS,10aS)-

The title compound of this example was prepared by procedures analogous to those described above in Example 136. Mass: 366 (M+1)⁺.

Examples 434-435

The title compounds of Examples 434-435 were prepared by procedures analogous to those described above in Example 9.

Example 434 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-2-[3-[(tetrahydro-2H-pyran-2-yl)oxy]-1-propynyl]-, (4aS,10aS)-, Mass: 481 (M+18)⁺.

Example 435 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-2-[3-[(tetrahydro-2H-pyran-2-yl)oxy]-1-propynyl]-, (4aS,10aS)-, Mass: 481 (M+18)⁺.

Examples 436-438

The title compounds of Examples 436-438 were prepared by procedures analogous to those described above in Example 136.

- Example 436 2,7-Phenanthrenediol, 2-butyl-1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-, (4a*S*,10a*S*)-, Mass: 380 (M).
- Example 437 2,7-Phenanthrenediol, 2-butyl-1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-, (4a*S*,10a*S*)-, Mass: 381 (M+1)⁺.
- Example 438 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[3-[(1-methyl-4-piperidinyl)amino]phenyl]methyl]-2-propyl-, (4a*S*,10a*R*)-, Mass: 463 (M+1)⁺.
- Example 439 2,7-Phenanthrenediol, 4a-[(3-aminophenyl)methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, (4a*S*,10a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 362 (M+1)⁺.

Examples 440-442

The title compounds of Examples 440-442 were prepared by procedures analogous to those described above in Example 136.

- Example 440 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[3-(methylamino)phenyl]methyl]-2-propyl-, (4a*S*,10a*S*)-, Mass: 380 (M+1)⁺.
- Example 441 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[3-[(1-methylethyl)amino]phenyl]methyl]-2-propyl-, (4a*S*,10a*R*)-, Mass: 408 (M+1)⁺.
- Example 442 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[3-[(1-methylethyl)amino]phenyl]methyl]-2-propyl-, (4a*S*,10a*R*)-, Mass: 408 (M+1)⁺.

Examples 443-444

The title compounds of Examples 443-444 were prepared by procedures analogous to those described above in Example 9.

- Example 443 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[3-[(1-methylethyl)amino]phenyl]methyl]-2-(1-propynyl)-, (4a*S*,10a*S*)-, Mass: 404 (M+1)⁺.

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Example 444 2,7-Phenanthrenediol, 2-ethynyl-1,2,3,4,4a,9,10,10a-octahydro-4a-[[3-[(1-methylethyl)amino]phenyl]methyl]-, (4a*S*,10a*S*)-, Mass: 390 (M+1)⁺.

Example 445 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-[(methylsulfonyl)oxy]phenyl]methyl]-2-propyl-, (4a*S*,10a*S*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 136. Mass: 462 (M+14)⁺.

Examples 446-447

The title compounds of Examples 446-447 were prepared by procedures analogous to those described above in Example 77.

Example 446 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-(phenylmethyl)-, *O*-ethyloxime, (4a*S*-*trans*)-, Mass: 350 (M+1)⁺.

Example 447 2(1*H*)-Phenanthrenone, 3,4,4a,9,10,10a-hexahydro-7-hydroxy-4a-(phenylmethyl)-, *O*-ethyloxime, (4a*S*-*trans*)-, Mass: 350 (M+1)⁺.

Examples 448-449

The title compounds of Examples 448-449 were prepared by procedures analogous to those described above in Example 9.

Example 448 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(2-pyridinylethynyl)-, (4a*S*,10a*R*)-, Mass: 410 (M+1)⁺.

Example 449 2,7-Phenanthrenediol, 4a-[[3-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, (4a*S*,10a*R*)-, Mass: 390 (M+1)⁺.

Example 450 2-Phenanthrenol, 4b-[[3-(dimethylamino)phenyl]methyl]-7,7-diethoxy-4b,5,6,7,8,8a,9,10-octahydro-, (4b*S*-*trans*)-

The title compound of this example was prepared by procedures analogous to those described above Preparation 5. Mass: 424 (M+1)⁺.

Example 451 2-Phenanthrenol, 7,7-diethoxy-4b,5,6,7,8,8a,9,10-octahydro-4b-(phenylmethyl)-, (4b*S*-*trans*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 77. Mass: 335 (M-45)⁺.

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Example 452 2,7-Phenanthrenediol, 2-[3-(dimethylamino)-1-propynyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-,
(4a*S*,10a*R*)-

The title compound of this example was prepared by procedures analogous to
those described above in Example 9. Mass: 390 (M+1)⁺.

Example 453 2(1*H*)-Phenanthrenone, 4a-[[3-(dimethylamino)phenyl]methyl]-
3,4,4a,9,10,10a-hexahydro-7-hydroxy-, *O*-ethyloxime, (4a*S*-
trans)-

The title compound of this example was prepared by procedures analogous to
those described above in Example 77. Mass: 393 (M+1)⁺.

Examples 454-456

The title compounds of Examples 454-456 were prepared by procedures
analogous to those described above in Example 136.

Example 454 2,7-Phenanthrenediol, 4a-[(4-aminophenyl)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-2-propyl-, (4a*S*,10a*S*)-, Mass:
348 (M-17)⁺.

Example 455 Acetamide, *N*-[4-[(1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-
propyl-4a(2*H*)-phenanthrenyl)methyl]phenyl]-, (4a*S*,10a*S*)-,
Mass: 407 (M).

Example 456 Acetamide, *N*-[3-[[2-(acetyloxy)-1,3,4,9,10,10a-hexahydro-7-
hydroxy-2-propyl-4a(2*H*)-phenanthrenyl)methyl]phenyl]-,
(4a*S*,10a*S*)-, Mass: 450 (M+1)⁺.

Example 457 2,7-Phenanthrenediol, 4a-[[4-(dimethylamino)phenyl]methyl]-
1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, (4a*S*,10a*R*)-

The title compound of this example was prepared by procedures analogous to
those described above Example 9. Mass: 390 (M+1)⁺.

Example 458 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-
[(1-methylethyl)amino]phenyl]methyl]-2-propyl-, (4a*S*,10a*S*)-

The title compound of this example was prepared by procedures analogous to
those described above in Example 136. Mass: 408 (M+1)⁺.

Example 459 Carbamic acid, dimethyl-, 7-(chloroethynyl)-4b,5,6,7,8a,9,10-
octahydro-7-hydroxy-4b-(phenylmethyl)-2-phenanthrenyl ester,
(4b*S*,8a*R*)-

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The title compound of this example was prepared by procedures analogous to those described above in Example 58. Mass: 438 (M+1)⁺.

Example 460 Acetamide, *N*-[3-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, [2*R*-(2α,4α,10αβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 386 (M-17)⁺.

Example 461 1-Pyrrolidinecarboxylic acid, 7-(chloroethynyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-2-phenanthrenyl ester, (4b*S*,8a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 58. Mass: 464 (M).

Examples 462-465

The title compounds of Examples 462-465 were prepared by procedures analogous to those described above in Example 136.

Example 462 Cyanamide, [3-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-propyl-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, (4a*S*,10a*S*)-, Mass: 389 (M-1)⁺

Example 463 Cyanamide, [3-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-propyl-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, (4a*S*,10a*S*)-, Mass: 389 (M-1)⁺

Example 464 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-propyl-4a-[[3-[[tetrahydro-2*H*-pyran-4-yl]amino]phenyl]methyl]-, (4a*S*,10a*S*)-, Mass: 450 (M+1)⁺

Example 465 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-propyl-4a-[[3-[[tetrahydro-2*H*-pyran-4-yl]amino]phenyl]methyl]-, (4a*S*,10a*S*)-, Mass: 450 (M+1)⁺

Example 466 Carbamic acid, dimethyl-, 4-[[7-[[dimethylamino]carbonyl]oxy]-1,3,4,9,10,10a-hexahydro-2-hydroxy-2-propyl-4a(2*H*)-phenanthrenyl]methyl]phenyl ester, (4a*S*,10a*S*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 58. Mass: 526 (M+18)⁺.

Example 467 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[[4-[[1-methylethyl]amino]phenyl]methyl]-2-propyl-, (4a*S*,10a*S*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 136. Mass: 408 (M+1)⁺.

Example 468 2(1*H*)-Phenanthrenone, 4a-[(3-aminophenyl)methyl]-3,4,4a,9,10,10a-hexahydro-7-hydroxy-, *O*-ethyloxime, (4a*S*-*trans*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 77. Mass: 365 (M+1)⁺.

Example 469 Carbamic acid, dimethyl-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-[[4-[(1-methylethyl)amino]phenyl]methyl]-7-propyl-2-phenanthrenyl ester, (4b*S*,8a*S*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 58. Mass: 479 (M+1)⁺.

Example 470 2-Phenanthrenol, 4b-[(3-aminophenyl)methyl]-7-(ethoxyamino)-4b,5,6,7,8,8a,9,10-octahydro-, (4b*S*,8a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 10. Mass: 367 (M+1)⁺.

Examples 471-472

The title compounds of Examples 471-472 were prepared by procedures analogous to those described above in Examples 58.

Example 471 Carbamic acid, dimethyl-, 4b-[(3-aminophenyl)methyl]-7-(ethoxyimino)-4b,5,6,7,8,8a,9,10-octahydro-2-phenanthrenyl ester, (4a*S*-*trans*)-, Mass: 436 (M+1)⁺.

Example 472 Carbamic acid, dimethyl-, 4b-[[3-[[[(dimethylamino)carbonyl]amino]phenyl]methyl]-7-(ethoxyimino)-4b,5,6,7,8,8a,9,10-octahydro-2-phenanthrenyl ester, (4a*S*-*trans*)-, Mass: 407 (M+1)⁺.

Example 473 2,7-Phenanthrenediol, 4a-[[4-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, (4a*S*,10a*S*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 390 (M+1)⁺.

Example 474 Carbamic acid, dimethyl-, 4b-[[4-(dimethylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, (4b*S*,8a*R*)-

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The title compound of this example was prepared by procedures analogous to those described above in Example 58. Mass: 461 (M+1)⁺.

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Example 475 2-Phenanthrenol, 4b-[[3-(dimethylamino)phenyl]methyl]-7-(ethylamino)-4b,5,6,7,8,8a,9,10-octahydro-, (4bS,8aS)-

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The title compound of this example was prepared by procedures analogous to those described above in Preparation 4. Mass: 379 (M+1)⁺.

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Example 476 Acetamide, N-[4a-[[3-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-7-hydroxy-3-phenanthrenyl]-N-ethyl-, (4aR,10aS)-

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The title compound of this example was prepared by procedures analogous to those described above in Example 47. Mass: 421 (M+1)⁺.

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Example 477 Acetamide, N-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2H)-phenanthrenyl]methyl]phenyl]-, (4aS,10aR)-

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The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 404 (M+1)⁺.

Examples 478-479

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The title compounds of Examples 478-479 were prepared by procedures analogous to those described above in Example 58.

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Example 478 1-Piperazinecarboxylic acid, 4-methyl-, 4b-[[3-(dimethylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, (4bS,8aR)-, Mass: 516 (M+1)⁺

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Example 479 2,7-Phenanthrenediol, 4a-[[3-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, 7-carbamate, (4aS,10aR)-, Mass: 433 (M+1)⁺

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Example 480 4-Morpholinecarboxamide, N-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2H)-phenanthrenyl]methyl]phenyl]-, [2R-(2α,4α,10αβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 476 (M+2)⁺.

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Example 481 Carbamic acid, [3-(dimethylamino)propyl]-, 4b-[[3-(dimethylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, (4bS,8aR)-

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The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 518 (M+1)⁺.

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Example 482 Acetamide, *N*-[4-[[7-[(aminocarbonyloxy)-1,3,4,9,10,10a-hexahydro-2-hydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, (4a*S*,10a*R*)-

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The title compound of this example was prepared by procedures analogous to those described above in Example 55. Mass: 447 (M+1)⁺.

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Example 483 Benzonitrile, 4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-propyl-4a(2*H*)-phenanthrenyl]methyl]-, (4a*S*,10a*S*)-

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The title compound of this example was prepared by procedures analogous to those described above or below in Example 136. Mass: 375 (M).

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Examples 484-487

The title compounds of Examples 484-487 were prepared by procedures analogous to those described above in Example 59.

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Example 484 Carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b-[[3-(dimethylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4bα,7α,8aβ)]-, Mass: 530 (M+1)⁺.

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Example 485 1-Piperidinecarboxylic acid, 4-(dimethylamino)-, 4b-[[3-(dimethylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4bα,7α,8aβ)]-, Mass: 544 (M+1)⁺.

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Example 486 1-Piperazinecarboxylic acid, 4-acetyl-, 4b-[[3-(dimethylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4bα,7α,8aβ)]-, Mass: 544 (M+1)⁺.

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Example 487 2,7-Phenanthrenediol, 4a-[[3-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, 7-(methylcarbamate), [2*R*-(2α,4α,10aβ)]-, Mass: 447 (M+1)⁺.

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Examples 488-489

The title compounds of Examples 488-489 were prepared by procedures analogous to those described above in Example 6.

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Example 488 2(1*H*)-Phenanthrenone, 4a-[[3-(dimethylamino)phenyl]methyl]-3,4,4a,9,10,10a-hexahydro-7-hydroxy-, (4a*S-trans*)-, Mass: 350 (M+1)⁺.

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Example 489 Carbamic acid, [4-[(1,3,4,9,10,10a-hexahydro-7-hydroxy-2-oxo-4a(2*H*)-phenanthrenyl)methyl]phenyl]-, 1,1-dimethylethyl ester, (4a*S-trans*)-, Mass: 423 (M+2)⁺.

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Example 490 Carbamic acid, 1*H*-1,2,4-triazol-3-yl-, 4b-[[3-(dimethylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, (4b*S,8aR*)-

10 The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 500 (M+1)⁺.

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Example 491 2,7-Phenanthrenediol, 4a-[[3-(dimethylamino)phenyl]methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-propyl-, [2*R*-(2α,4α,10α)]-

25 The title compound of this example was prepared by procedures analogous to those described above in Example 136. Mass: 395 (M+2)⁺.

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Examples 492-495

The title compounds of Examples 492-495 were prepared by procedures analogous to those described above in Example 9.

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Example 492 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-[(4-hydroxyphenyl)methyl]-2-(1-propynyl)-, [2*R*-(2α,4α,10αβ)]-, Mass: 362 (M).

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Example 493 Glycine, *N*-[3-[[1,3,4,9,10,10a-hexahydro-2-hydroxy-7-(2-methoxy-2-oxoethoxy)-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-*N*-methyl-, methyl ester, [2*R*-(2α,4α,10αβ)]-, Mass: 521 (M+2)⁺.

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Example 494 Glycine, *N*-[3-[[1,3,4,9,10,10a-hexahydro-2-hydroxy-7-(2-methoxy-2-oxoethoxy)-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-*N*-(2-methoxy-2-oxoethyl)-, methyl ester, [2*R*-(2α,4α,10αβ)]-, Mass: 579 (M+2)⁺.

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Example 495 Urea, *N*-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-*N,N*-dimethyl-, [2*R*-(2α,4α,10αβ)]-, Mass: 435 (M+2)⁺.

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Example 496 Acetamide, 2-[[3-[[7-(2-amino-2-oxoethoxy)-1,3,4,9,10,10a-hexahydro-2-hydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]methylamino]-, [2*R*-(2α,4α,10αβ)]-

5 The title compound of this example was prepared by procedures analogous to those described above in Example 55. Mass: 491 (M+2)⁺.

15 Examples 497-499

 The title compounds of Examples 497-499 were prepared by procedures analogous to those described above in Example 9.

10 Example 497 Methanesulfonamide, *N*-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, [2*R*-(2α,4α,10αβ)]-, Mass: 442 (M+3)⁺.

25 Example 498 Acetamide, *N*-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, [2*R*-(2α,4α,10αβ)]-, Mass: 404 (M+1)⁺.

15 Example 499 Acetamide, *N*-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, [2*R*-(2α,4α,10αβ)]-, Mass: 404 (M+1)⁺.

30 20 Example 500 Carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4bα,7α,8aβ)]-

35 The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 470 (M-16)⁺.

25 Example 501 2-Pyridinecarboxamide, *N*-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, [2*R*-(2α,4α,10αβ)]-

40 The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 434 (M-32)⁺.

45 30 Example 502 Carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, monohydrochloride, [4b*S*-(4bα,7α,8aβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 506 (M-17)⁺.

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Example 503 5-Isoxazolecarboxamide, *N*-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, [2*R*-(2α,4α,10aβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 459 (M+3)⁺.

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Example 504 Acetamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4bα,7α,8aβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 55. Mass: 404 (M+1)⁺.

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Example 505 1(2*H*)-Pyrimidineacetamide, *N*-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-3,4-dihydro-5-methyl-2,4-dioxo-, [2*R*-(2α,4α,10aβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 546 (M+18)⁺.

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Example 506 Carbamic acid, dimethyl-, 2-[[7-[[[(dimethylamino)carbonyl]oxy]-4b-[[3-(dimethylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-(1-propynyl)-2-phenanthrenyl]oxy]ethyl ester, [4b*S*-(4bα,7α,8aβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 576 (M+1)⁺.

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Example 507 Acetamide, *N*-[2-(dimethylamino)ethyl]-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4bα,7α,8aβ)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 244. Mass: 476 (M+2)⁺.

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Examples 508-511

The title compounds of Examples 508-511 were prepared by procedures analogous to those described above in Example 59.

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Example 508 Carbamic acid, [3-(dimethylamino)propyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-, Mass: 457 (M-17)*.

Example 509 Carbamic acid, dimethyl-, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-2,7-phenanthrenediyl ester, [2R-(2 α ,4a α ,10a β)]-, Mass: 489 (M+1)*.

Example 510 Carbamic acid, [2-(4-morpholinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-, Mass: 485 (M-17)*.

Example 511 Carbamic acid, [3-(1H-imidazol-1-yl)propyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-, Mass: 498 (M+1)*.

Example 512 Acetic acid, [[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, methyl ester, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 54. Mass: 418 (M).

Example 513 1H-Imidazole-4-sulfonamide, N-[4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2H)-phenanthrenyl]methyl]phenyl]-1-methyl-, [2R-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 523 (M+18)*.

Example 514 Acetamide, N-[2-(4-morpholinyl)ethyl]-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. Mass: 517 (M+1)*.

Example 515 Acetamide, 2,2'-[[1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-2,7-phenanthrenediyl]bis(oxy)]bis-, [2R-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 55. Mass: 459 (M-1)*.

Example 516 Acetamide, *N*-[3-(1*H*-imidazol-1-yl)propyl]-2-
[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-
(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to
those described above in Example 244. Mass: 512 (M+1)⁺.

Example 517 Carbamic acid, [2-(dimethylamino)ethyl]-, 4b,5,6,7,8,8a,9,10-
octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-
phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to
those described above in Example 59. Mass: 461 (M+1)⁺.

Example 518 Carbamic acid, [2-(dimethylamino)ethyl]-, 4b,5,6,7,8,8a,9,10-
octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-
phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-HCl

The title product of this example is the HCl salt of the title product of Example
517. Mass: 498 (M+1)⁺.

Examples 519-523

The title compounds of Examples 519-523 were prepared by procedures
analogous to those described above in Example 244.

Example 519 Acetamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-
(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-*N*-[2-(3-
pyridinyl)ethyl]-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 509 (M+1)⁺.

Example 520 Piperazine, 1-methyl-4-[[[4b,5,6,7,8,8a,9,10-octahydro-7-
hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-
phenanthrenyl]oxy]acetyl]-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 487
(M+1)⁺.

Example 521 Acetamide, *N*-[3-(4-methyl-1-piperazinyl)propyl]-2-
[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-
(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass:
544 (M+1)⁺.

Example 522 Piperidine, 1-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-
(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]acetyl]-4-
(1-pyrrolidinyl)-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 541 (M+1)⁺.

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- Example 523 Acetamide, *N*-methoxy-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 432 (M-1)⁺.
- Example 524 2-Phenanthrenol, 7-[(4,5-dihydro-1*H*-imidazol-2-yl)methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10a β)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 429 (M+1)⁺.

Examples 525-526

- 10 The title compounds of Examples 525-526 were prepared by procedures analogous to those described above in Example 59.

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- Example 525 Carbamic acid, [3-(1-pyrrolidinyl)propyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 501 (M+1)⁺.
- Example 526 Acetamide, *N*-hydroxy-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 418 (M-1)⁺.

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Examples 527-528

- 20 The title compounds of Examples 527-528 were prepared by procedures analogous to those described above in Example 67.

- Example 527 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[2-(1-pyrrolidinyl)ethoxy]-, Mass: 444 (M+1)⁺; isomer of title compound of Example 528.
- Example 528 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[2-(1-pyrrolidinyl)ethoxy]-, Mass: 444 (M+1)⁺; isomer of title compound of Example 527.

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Examples 529-535

The title compounds of Examples 529-535- were prepared by procedures analogous to those described above in Example 244.

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- Example 529 Acetamide, *N*-(methylsulfonyl)-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 480 (M-1)⁺.

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Example 530 Acetamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-N-(2-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 495 (M+1)⁺.

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Example 531 Acetamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-N-(3-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 495 (M+1)⁺.

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Example 532 Acetamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-N-3-pyridinyl-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 481 (M+1)⁺.

10 Example 533

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Acetamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-N-pyrazinyl-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 482 (M+1)⁺.

Example 534 Ethanimidamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 403 (M+1)⁺.

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Example 535 Carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b-[[4-(acetylamino)phenyl]methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-, Mass: 544 (M+1)⁺.

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Example 536 Carbamothioic acid, dimethyl-, O-[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl] ester, [4bS-(4b α ,7 α ,8a β)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 434 (M+1)⁺.

25 Examples 537-538

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The title compounds of Examples 537-538 were prepared by procedures analogous to those described in Example 74.

Example 537 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-pyrimidinyl)-, [2R-(2 α ,4a α ,10a β)]-, Mass: 425 (M+1)⁺.

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Example 538 2-Phenanthrenol, 7-[(2-amino-6-methyl-4-pyrimidinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2R-(2 α ,4a α ,10a β)]-, Mass: 454 (M+1)⁺.

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Example 539 Acetamide, *N*-[2-(1-methyl-2-pyrrolidinyl)ethyl]-2-
[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-
(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. Mass: 515 (M+1)⁺.

Example 540 Carbamic acid, [2-(1-methyl-2-pyrrolidinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-
(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 501 (M+1)⁺.

Example 541 3-Pyridinecarboxamide, 6-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 467 (M+1)⁺.

Example 542 Carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(2-propenyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 437 (M+1)⁺.

Examples 543-544

The title compounds of Examples 543-544 were prepared by procedures analogous to those described above in Example 69.

Example 543 2-Phenanthrenol, 7-[[5-[2-(dimethylamino)ethyl]-1,2,4-oxadiazol-3-yl]methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-, Mass: 500 (M+1)⁺.

Example 544 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-[[5-(1-piperidinylmethyl)-1,2,4-oxadiazol-3-yl]methoxy]-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-, Mass: 526 (M+1)⁺.

Example 545 2-Phenanthrenol, 7-[(4,6-dimethoxy-1,3,5-triazin-2-yl)oxy]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-
propynyl)-, [2*R*-(2 α ,4 α ,10 α)]-

The title compound of this example was prepared by procedures analogous to
those described above in Example 74. Mass: 486 (M+1)⁺.

Examples 546-547

The title compounds of Examples 546-547 were prepared by procedures
analogous to those described above in Example 72.

Example 546 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
(phenylmethyl)-7-[[3-(1-piperidinylmethyl)-1,2,4-oxadiazol-5-
yl]methoxy]-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α)]-, Mass: 526
(M+1)⁺.

Example 547 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
(phenylmethyl)-2-(1-propynyl)-7-[[3-(2-pyridinyl)-1,2,4-
oxadiazol-5-yl]methoxy]-, [2*R*-(2 α ,4 α ,10 α)]-, Mass: 506
(M+1)⁺.

Examples 548-550

The title compounds of Examples 548-550 were prepared by procedures
analogous to those described above in Example 59.

Example 548 Carbamic acid, [2-(3-pyridinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-
octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-
phenanthrenyl ester, [4*bS*-(4 α ,7 α ,8 α)]-, Mass: 495 (M+1)⁺.

Example 549 Carbamic acid, (2-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-
octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-
phenanthrenyl ester, [4*bS*-(4 α ,7 α ,8 α)]-, Mass: 481 (M+1)⁺.

Example 550 Carbamic acid, [2-(2-pyridinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-
octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-
phenanthrenyl ester, [4*bS*-(4 α ,7 α ,8 α)]-, Mass: 495 (M+1)⁺.

Example 551 2-Phenanthrenol, 4b,5,6,7,8,8a,9,10-octahydro-4b-pentyl-7-
propyl-, (4*bR*,8 α *R*)-

The title compound of this example was prepared by procedures analogous to
those described above in Example 10. Mass: 313 (M-1)⁺.

Examples 552-553

The title compounds of Examples 552-553 were prepared by procedures analogous to those described above in Example 59.

Example 552 Carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-propyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-, Mass: 439 (M+1)⁺.

Example 553 Carbamic acid, [2-(dimethylamino)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-propyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-, Mass: 413 (M+1)⁺.

Example 554 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-7-(pyrazinyloxy)-, [2*R*-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 377 (M+1)⁺.

Example 555 Carbamic acid, (1*H*-tetrazol-5-ylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 470 (M-1)⁺.

Example 556 2-Phenanthrenol, 7-[(4-chloro-2-pyrimidinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 460 (M+1)⁺.

Examples 557-558

The title compounds of Examples 557-558 were prepared by procedures analogous to those described above in Example 72.

Example 557 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[[3-(1-piperidinylmethyl)-1,2,4-oxadiazol-5-yl]methoxy]-4a-propyl-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-, Mass: 478 (M+1)⁺.

Example 558 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-7-[[3-(2-pyridinyl)-1,2,4-oxadiazol-5-yl]methoxy]-, [2*R*-(2 α ,4a α ,10a β)]-, Mass: 458 (M+1)⁺.

Examples 559-561

The title compounds of Examples 559-561 were prepared by procedures analogous to those described above in Example 59.

Example 559 Carbamic acid, (4-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 481 (M+1)⁺.

Example 560 Carbamic acid, (3-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 481 (M+1)⁺.

Example 561 Carbamic acid, (3-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-propyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-, Mass: 433 (M+1)⁺.

Example 562 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(5-methoxy-2-pyrimidinyl)oxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 455 (M+1)⁺.

Example 563 Morpholine, 4-[[6-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-3-pyridinyl]carbonyl]-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. Mass: 537 (M+1)⁺.

Examples 564-565

The title compounds of Examples 564-565 were prepared by procedures analogous to those described above in Example 59.

Example 564 Carbamic acid, (2-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-propyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-, Mass: 433 (M+1)⁺.

Example 565 Carbamic acid, (4-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-propyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)]-, Mass: 433 (M+1)⁺.

Example 566 2-Phenanthrenol, 7-[(5-amino-1*H*-1,2,4-triazol-3-yl)methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 62.

Examples 567-568

The title compounds of Examples 567-568 were prepared by procedures analogous to those described above in Example 76. Mass: 395 (M+1)⁺.

Example 567 Pyridine, 3,3'-[[1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-2,7-phenanthrenediyl]bis(oxymethylene)]bis-, [2*R*-(2α,4α,10αβ)]-, Mass: 529 (M+1)⁺.

Example 568 Pyridine, 4,4'-[[1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-2,7-phenanthrenediyl]bis(oxymethylene)]bis-, [2*R*-(2α,4α,10αβ)]-, Mass: 529 (M+1)⁺.

Example 569 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(4-pyridinylmethoxy)-, [2*R*-(2α,4α,10αβ)]

The title compound was obtained as described in Example 76, except 4-picoyl chloride hydrochloride was used instead of 3-picoyl chloride hydrochloride. MS *m/z* 438 (M+H)⁺.

Example 570 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-propyl-, [2*R*-(2α,4α,10α)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 10. Mass: 313 (M-17)⁺.

Example 571 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-(1-propynyl)-7-(pyrazinyloxy)-, [2*R*-(2α,4α,10αβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 405 (M+1)⁺.

Example 572 Carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-pentyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4bα,7α,8aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 467 (M+1)⁺.

Example 573 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-propyl-2-(1-propynyl)-7-(4-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 390 (M+1)⁺.

Example 574 Carbamic acid, [2-(4-pyridinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 59. Mass: 495 (M+1)⁺.

Example 575 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-(1-propynyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-

To a solution of 50 mg of the title compound of Example 252 and 9.2 mg of 60% NaH in 2 mL of anhydrous DMF was added 30 mg of 2-picolyl chloride hydrochloride at RT under N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC SiO₂ using 4% MeOH in CH₂Cl₂ as the elutant afforded 40 mg (65%) of the title product of this example as white fluffy powder. Mass: 419 (M+2)⁺.

Examples 576-577

The title compounds of Examples 576-577 were prepared by procedures analogous to those described above in Example 244.

Example 576 Acetamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-*N*-[2-(4-pyridinyl)ethyl]-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 509 (M+1)⁺.

Example 577 Acetamide, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-*N*-[2-(2-pyridinyl)ethyl]-, [4b*S*-(4b α ,7 α ,8a β)]-, Mass: 509 (M+1)⁺.

Example 578 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]

The title compound was obtained as described in Example 76, except 2-picolyl chloride hydrochloride was used instead of 3-picolyl chloride hydrochloride. MS *m/z* 438 (M+H)⁺.

Examples 579-580

The title compounds of Examples 579-580 were prepared by procedures analogous to those described above in Example 59.

- Example 579 Carbamic acid, [2-(2-pyridinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-pentyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)], Mass: 476 (M+2)⁺.
- Example 580 Carbamic acid, [2-(4-morpholinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-pentyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)], Mass: 483 (M+1)⁺.
- Example 581 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[2-(4-morpholinyl)ethoxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 67. Mass: 460 (M+1)⁺.

- Example 582 2-Phenanthrenol, 7-[(2,6-dimethoxy-4-pyrimidinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 485 (M+1)⁺.

Examples 583-584

The title compounds of Examples 583-584 were prepared by procedures analogous to those described above in Example 59.

- Example 583 Carbamic acid, (4-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-pentyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)], Mass: 461 (M+1)⁺.
- Example 584 Carbamic acid, (3-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-pentyl-7-(1-propynyl)-2-phenanthrenyl ester, [4b*R*-(4b α ,7 α ,8a β)], Mass: 461 (M+1)⁺.

Examples 585-588

The title compounds of Examples 585-586 were prepared by procedures analogous to those described above in Example 75.

- Example 585 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[[3-(1-

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pyrrolidinyl)pyrazinyl]oxy)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 494 (M+1)⁺.

Example 586 2-Phenanthrenol, 1,2,3,4,4 α ,9,10,10 α -octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[[6-(1-pyrrolidinyl)-4-pyrimidinyl]oxy]-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 494 (M+1)⁺.

Example 587 2-Phenanthrenol, 1,2,3,4,4 α ,9,10,10 α -octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[[6-(1-pyrrolidinyl)-2-pyridinyl]oxy]-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 493 (M+1)⁺.

Example 588 2-Phenanthrenol, 1,2,3,4,4 α ,9,10,10 α -octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[[6-(1-pyrrolidinyl)pyrazinyl]oxy]-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 494 (M+1)⁺.

Example 589 2-Phenanthrenol, 1,2,3,4,4 α ,9,10,10 α -octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(pyrazinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 439 (M+1)⁺.

Examples 590-591

The title compounds of Examples 590-591 were prepared by procedures analogous to those described above in Example 67.

Example 590 2-Phenanthrenol, 1,2,3,4,4 α ,9,10,10 α -octahydro-4a-(phenylmethyl)-7-[2-(1-piperazinyl)ethoxy]-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 459 (M+1)⁺.

Example 591 Piperazine, 1-acetyl-4-[2-[[4b,5,6,7,8,8 α ,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]ethyl]-, [4b*S*-(4b α ,7 α ,8 α β)]-, Mass: 501 (M+1)⁺.

Example 592 2-Phenanthrenol, 1,2,3,4,4 α ,9,10,10 α -octahydro-4a-pentyl-2-(1-propynyl)-7-(2-pyrimidinyl)oxy)-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 405 (M+1)⁺.

Example 593 2-Phenanthrenol, 1,2,3,4,4 α ,9,10,10 α -octahydro-4a-pentyl-2-(1-propynyl)-7-(pyrazinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-

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The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 419 (M+1)⁺.

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Example 594 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-(1-propynyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-

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The title compound was obtained as described in Example 575, except 3-picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride. Mass: 418 (M+1)⁺

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Example 595 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-(1-propynyl)-7-(4-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]

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The title compound was obtained as described in Example 575, except 4-picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride. Mass: 418 (M+1)⁺.

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Examples 596-599

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The title compounds of Examples 596-599 were prepared by procedures analogous to those described above in Example 67.

Example 596 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethoxy]-, [2*R*-(2α,4α,10aβ)]-, Mass: 537 (M+1)⁺.

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Example 597 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[2-(4-pyridinylamino)ethoxy]-, Mass: 467 (M+1)⁺; isomer of title compound of Example 598.

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Example 598 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[2-(4-pyridinylamino)ethoxy]-, Mass: 467 (M+1)⁺; isomer of title compound of Example 597.

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Example 599 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[2-(4-morpholinyl)ethoxy]-4a-pentyl-2-(1-propynyl)-, [2*R*-(2α,4α,10aβ)]-, Mass: 441 (M+2)⁺.

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Examples 600-601

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The title compounds of Examples 600-601 were prepared by procedures analogous to those described above in Example 76.

Example 600 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-(1-propynyl)-7-(5-pyrimidinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-, Mass: 419 (M+1)⁺.

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Example 601 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(4-pyrimidinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-, Mass: 439 (M+1)⁺.

Examples 602-603

5 The title compounds of Examples 602-603 were prepared by procedures analogous to those described above in Example 75.

15 Example 602 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[[2-(1-pyrrolidinyl)-4-pyridinyl]methoxy]-, [2*R*-(2α,4α,10aβ)]-, Mass: 507 (M+1)⁺.

10 Example 603 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-(1-propynyl)-7-[[6-(1-pyrrolidinyl)-3-pyridinyl]methoxy]-, [2*R*-(2α,4α,10aβ)]-, Mass: 487 (M+1)⁺.

Example 604 2-Phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-pentyl-7-(1-propynyl)-, [4b*R*-(4bα,7α,8aβ)]-

15 The title compound of this example was prepared by procedures analogous to those described above in Example 15. Mass: 335 (M).

Example 605 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[2-(4-morpholinyl)ethoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-

20 The title compound of this example was prepared by procedures analogous to those described above in Example 67. Mass: 464 (M+1)⁺.

Example 606 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[2-(4-morpholinyl)ethoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-HCl

25 The title product of this example is the HCl salt of the title product of Example 605. Mass: 464 (M+1-HCl)+.

Example 607 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[2-(4-morpholinyl)ethoxy]-2,4a-dipropyl-, [2*R*-(2α,4α,10aβ)]-

30 The title compound of this example was prepared by procedures analogous to those described above in Example 67. Mass: 416 (M+1)⁺.

Examples 608-609

The title compounds of Examples 608-609 were prepared by procedures analogous to those described above in Example 76.

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Example 608 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-7-(2-piperidinylmethoxy)-2-propyl-, [2*R*-(2 α ,4 α ,10a β)]-, Mass: 428 (M+1)⁺.

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Example 609 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-[1-(4-pyridinyl)ethoxy]-, [2*R*-(2 α ,4 α ,10a β)]-, Mass: 456 (M+1)⁺.

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Example 610 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[2-(4-morpholinyl)ethoxy]-4a-pentyl-2-propyl-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 67. Mass: 444 (M+1)⁺.

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Example 611 Acetamide, *N*-[2-(4-morpholinyl)ethyl]-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. Mass: 521 (M+1)⁺.

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Example 612 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-pentyl-2-propyl-7-(4-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 422 (M+1)⁺.

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Examples 613-614

The title compounds of Examples 613-614 were prepared by procedures analogous to those described above in Example 15.

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Example 613 2-Phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-methoxy-4b-pentyl-7-(1-propynyl)-, [4b*R*-(4b α ,7 α ,8a β)]-, Mass: 367 (M+18)⁺.

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Example 614 2-Phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-methoxy-4b-pentyl-7-propyl-, [4b*R*-(4b α ,7 α ,8a β)]-, Mass: 371 (M+18)⁺.

Examples 615-619

The title compounds of Examples 615-619 were prepared by procedures analogous to those described above in Example 74.

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- Example 615 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(pyrazinyloxy)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 429 (M+1)⁺.
- Example 616 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(2-pyrimidinylloxy)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 429 (M+1)⁺.
- Example 617 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(3-methylpyrazinyl)oxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 439 (M+1)⁺.
- Example 618 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(3-methyl-2-quinoxalinyloxy)-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 489 (M+1)⁺.
- Example 619 2-Phenanthrenol, 7-[(3,6-dimethylpyrazinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 453 (M+1)⁺.
- Example 620 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α β)]-
- The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 452 (M+1)⁺.
- Example 621 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]
- The title compound was obtained as described in Example 627, below, except 2-methyl-3-picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride. Mass: 456 (M+1)⁺.
- Example 622 2-Phenanthrenol, 7-[(2-amino-6-methyl-4-pyrimidinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-
- The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 458 (M+1)⁺.

Example 623 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(6-methyl-2-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 456 (M+1)⁺.

Example 624 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(6-methyl-2-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2α,4α,10aβ)]

The title compound was obtained as described in Example 76, except 3-methyl-2-picolyl chloride hydrochloride was used instead of 3-picolyl chloride hydrochloride, yield 90%. MS *m/z* 452 (M+H)⁺.

Examples 625-626

The title compounds of Examples 625-626 were prepared by procedures analogous to those described above in Example 74.

Example 625 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-[[4-(trifluoromethyl)-2-pyrimidinyl]oxy]-, [2*R*-(2α,4α,10aβ)]-, Mass: 479 (M-17)⁺.

Example 626 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[[4-(trifluoromethyl)-2-pyrimidinyl]oxy]-, [2*R*-(2α,4α,10aβ)]-, Mass: 493 (M+1)⁺.

Example 627 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(2-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]

To a solution of 30 mg of the title compound of Example 10 and 8 mg of 60% NaH in 2 mL of anhydrous DMF was added 17 mg of 2-picolyl chloride hydrochloride at RT under N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC SiO₂ using 30% EtOAc in hexanes as the elutant afforded 32 mg (84%) of the title product of this example as white fluffy powder. Mass: 442 (M+1)⁺.

Example 628 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(3-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]

The title compound was obtained as described in Example 627, except the 3-picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride.

Mass: 442 (M+1)⁺.

Examples 629-633

The title compounds of Examples 629-633 were prepared by procedures analogous to those described above in Example 76.

Example 629 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(6-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-, Mass: 456 (M+1)⁺.

Example 630 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(6-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2α,4α,10aβ)]-, Mass: 452 (M+1)⁺.

Example 631 Pyridine, 3,3'-[[1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-2,7-phenanthrenediyl]bis(oxymethylene)]bis[6-methyl-, [2*R*-(2α,4α,10aβ)]-, Mass: 557 (M+1)⁺.

Example 632 2-Pyridinecarbonitrile, 6-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]methyl]-, [4b*S*-(4bα,7α,8aβ)]-, Mass: 467 (M+1)⁺.

Example 633 2-Pyridinecarbonitrile, 6-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]methyl]-, [4b*S*-(4bα,7α,8aβ)]-, Mass: 481 (M+18)⁺.

Examples 634-646

The title compounds of Examples 634-646 were prepared by procedures analogous to those described above in Example 74.

Example 634 2-Phenanthrenol, 7-[(3-amino-4-methyl-2-pyridinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-, Mass: 457 (M+1)⁺.

Example 635 2-Phenanthrenol, 7-[(3-amino-2-pyridinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-, Mass: 443 (M+1)⁺.

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Example 636

3-Pyridinecarbonitrile, 6-methyl-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 463 (M+1)⁺.

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Example 637

3-Pyridinecarbonitrile, 6-methyl-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 467 (M+1)⁺.

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Example 638

3-Pyridinecarbonitrile, 2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 453 (M+1)⁺.

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Example 639

2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-[2-(trifluoromethyl)phenoxy]-, [2R-(2 α ,4 α ,10a β)]-, Mass: 496 (M+1)⁺.

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Example 640

2-Pyridinecarbonitrile, 6-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, Mass: 449 (M+1)⁺.

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Example 641

2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-[[6-(trifluoromethyl)-2-pyridinyl]oxy]-, Mass: 492 (M+1)⁺.

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Example 642

2-Pyridinecarbonitrile, 6-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 471 (M+18)⁺.

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Example 643

3-Pyridinecarbonitrile, 4,6-dimethyl-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 477 (M+1)⁺.

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Example 644

3-Pyridinecarbonitrile, 6-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 449 (M+1)⁺.

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Example 645

3-Pyridinecarbonitrile, 6-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 453 (M+1)⁺.

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Example 646

3-Pyridinecarbonitrile, 4,6-dimethyl-2-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]-, [4bS-(4b α ,7 α ,8a β)]-, Mass: 481 (M+1)⁺.

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Examples 647-649

The title compounds of Examples 647-649 were prepared by procedures analogous to those described above in Example 76.

- Example 647 2-Phenanthrenol, 7-[(2,6-dichloro-4-pyrimidinyl)methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 511 (M).
- Example 648 2-Phenanthrenol, 7-[(2,6-dimethoxy-4-pyrimidinyl)methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 503 (M+1)*.
- Example 649 2-Phenanthrenol, 7-[(2-chloro-6-methyl-4-pyridinyl)methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 490 (M).
- Example 650 2-Phenanthrenol, 7-[(6-chloro-2-pyridinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 444 (M-18)*.

- Example 651 2-Pyridinecarbonitrile, 3-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl]oxy]methyl]-, [4b*S*-(4b α ,7 α ,8a β)]

The title compound was obtained as described in Example 76, except 2-cyano-3-picolyl chloride hydrochloride was used instead of 3-picolyl chloride hydrochloride, yield 90%. MS *m/z* 463 (M+H)*.

- Example 652 2-Pyridinecarbonitrile, 3-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]methyl]-, [4b*S*-(4b α ,7 α ,8a β)]

The title compound was obtained as described in Example 627, except 2-cyano-3-picolyl chloride hydrochloride was used instead of 2-picolyl chloride hydrochloride. Mass: 449 (M-17)*.

Examples 653-660

The title compounds of Examples 653-660 were prepared by procedures analogous to those described above in Example 76.

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- Example 653 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methoxy-6-methyl-4-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 486 (M+1)⁺.
- Example 654 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-4-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 456 (M+1)⁺.
- Example 655 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-quinolinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 488 (M+1)⁺.
- Example 656 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(2-quinolinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 492 (M+1)⁺.
- Example 657 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methoxy-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 472 (M+1)⁺.
- Example 658 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(pyrazinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 443 (M+1)⁺.
- Example 659 2(1*H*)-Pyridinone, 3-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]methyl]-, [4b*S*-(4b α ,7 α ,8 $\alpha\beta$)]-, Mass: 458 (M+1)⁺.
- Example 660 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(4-pyrimidinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 443 (M+1)⁺.
- Example 661 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methoxy-1-propynyl)-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 359 (M-17)⁺.

- Example 662 3-Pyridinecarboxamide, 6-methyl-2-[[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]-, [4b*S*-(4b α ,7 α ,8 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 485 (M+1)⁺.

Examples 663-665

The title compounds of Examples 663-665 were prepared by procedures analogous to those described above in Example 76.

- Example 663 2-Phenanthrenol, 7-[(4,6-dimethyl-2-pyrimidinyl)methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10a β)]-, Mass: 471 (M+1)*.
- Example 664 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(3-quinolinylmethoxy)-, [2*R*-(2 α ,4 α ,10a β)]-, Mass: 492 (M+1)*.
- Example 665 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(4-quinolinylmethoxy)-, [2*R*-(2 α ,4 α ,10a β)]-, Mass: 492 (M+1)*.
- Example 666 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(3-methyl-2-quinoxalinyloxy)-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 74. Mass: 493 (M+1)*.

- Example 667 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(5-methyl-3-isoxazolyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 428 (M-17)*.

- Example 668 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methoxypropyl)-4a-(phenylmethyl)-, [2*S*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 10. Mass: 363 (M-17)*.

- Example 669 2,7-Phenanthrenediol, 2-(ethoxyethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. Mass: 359 (M-17)*.

Examples 670-671

The title compounds of Examples 670-671 were prepared by procedures analogous to those described above in Example 10.

Example 670 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(3-phenyl-2-propynyl)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 405 (M-17)⁺.

Example 671 2,7-Phenanthrenediol, 2-(2-ethoxyethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 363 (M-17)⁺.

Example 672 3-Pyridinecarbonitrile, 6-[[4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-2-phenanthrenyl]oxy]methyl]-, [4b*S*-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 467 (M+1)⁺.

Example 673 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methoxypropyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*S*-(2 α ,4 α ,10 α β)]

To a solution of 28 mg of the title compound of Example 668 and 7 mg of 60% NaH in 2 mL of anhydrous DMF was added 15 mg of 3-picolyl chloride hydrochloride at RT under N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC SiO₂ using 35% EtOAc in hexanes as the eluant afforded 30 mg (87%) of the title product of this example as white fluffy powder. Mass: 472 (M+1)⁺.

Example 674 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(6-methoxy-2-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 472 (M+1)⁺.

Examples 675-677

The title compounds of Examples 675-677 were prepared by procedures analogous to those described above in Example 81.

Example 675 2,7-Phenanthrenediol, 2-[(cyclopropylmethoxy)methyl]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 375 (M-17)⁺.

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Example 676 2,7-Phenanthrenediol, 2-(ethoxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 349 (M-17)*.

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Example 677 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-[(2,2,2-trifluoroethoxy)methyl]-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 403 (M-17)*.

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Example 678 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(1-piperidinylmethyl)-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 83. Mass: 406 (M+1)*.

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Examples 679-682

The title compounds of Examples 679-682 were prepared by procedures analogous to those described above in Example 81.

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Example 679 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-[(2-(1-methylethoxy)ethoxy)methyl]-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 423 (M+1)*.

Example 680 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(methoxymethyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 444 (M+1)*.

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Example 681 2-Phenanthrenol, 2-(ethoxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, Mass: 458 (M+1)*.

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Example 682 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-[(2-methoxyethoxy)methyl]-4a-(phenylmethyl)-, (4*aS*,10*aR*)-, Mass: 397 (M+1)*.

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Example 683 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-5-thiazolyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. Mass: 462 (M+1)*.

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Examples 684-685

The title compounds of Examples 684-685 were prepared by procedures analogous to those described above in Example 72.

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Example 684 2-Phenanthrenol, 7-[[5-(1,1-dimethylethyl)-1,2,4-oxadiazol-3-yl]methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 489 (M+1)*.

Example 685 2-Phenanthrenol, 7-[[5-(3,5-dimethyl-4-isoxazolyl)-1,2,4-oxadiazol-3-yl]methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α β)]-, Mass: 510 (M-17)*.

Example 686 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methoxy-1-propynyl)-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above for the preparation of the title compound of Example 76. Mass: 468 (M+1)*.

Example 687 2-Phenanthrenol, 4b,5,6,10-tetrahydro-7-phenyl-4b-(phenylmethyl)-, (S)-

The title compound of this example was prepared by procedures analogous to those described above in Example 136. MS: 364 (M+1)*.

Examples 688-691

The title compounds of Examples 688-691 were prepared by procedures analogous to those described above in Example 51.

Example 688 2(1*H*)-Phenanthrenone, 4b-(2-butenyl)-3,4,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-7-(1-propynyl)-, [4b*S*-[4b α (*E*),7 α ,8a β]]-; See also Example 51.

Example 689 2(3*H*)-Phenanthrenone, 4b-(2-butenyl)-4,4a,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-7-(1-propynyl)-, [4b*S*(*E*),7*S*,8a*R*]-, MS: 312 (M+1)*.

Example 690 2(3*H*)-Phenanthrenone, 4b-(2-butenyl)-4,4a,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-7-(1-propynyl)-, [4a*R*-[4a α ,4b β (*E*),7 β ,8a α]]-; See also Example 51.

Example 691 2(1*H*)-Phenanthrenone, 4b-(2-butenyl)-3,4,4b,5,6,7,8,8a,9,10-decahydro-7-hydroxy-7-(1-propynyl)-, [4b*S*-[4b α (*E*),7 β ,8a β]]-, MS: 313 (M+1)*.

Example 692 2(3*H*)-Phenanthrenone, 4*b*-(2-butenyl)-
4,4*a*,4*b*,5,6,7,8,8*a*,9,10-decahydro-7-hydroxy-7-(1-propynyl)-,
oxime, [4*bS*(*E*),7*R*,8*aR*]-

The title compound of this example was prepared by procedures analogous to those described above in Example 77. MS: 328 (M+1)⁺.

Examples 693-695

The title compounds of Examples 693-695 were prepared by procedures analogous to those described above in Example 136.

Example 693 2-Phenanthrenol, 4*b*,5,6,8*a*,9,10-hexahydro-4*b*-[[4-hydroxyphenyl)methyl]-7-propyl-, (4*bS*-*cis*), MS: 349 (M+1)⁺.

Example 694 2,7-Phenanthrenediol, 4*a*-[[4-(dimethylamino)phenyl)methyl]-1,2,3,4,4*a*,9,10,10*a*-octahydro-2-propyl-, (4*aS*,10*aS*)-, MS: 370 (M+1)⁺; isomer of the title product of Example 695.

Example 695 2,7-Phenanthrenediol, 4*a*-[[4-(dimethylamino)phenyl)methyl]-1,2,3,4,4*a*,9,10,10*a*-octahydro-2-propyl-, (4*aS*,10*aS*)-, MS: 370 (M+1)⁺; isomer of the title product of Example 694.

Example 696 2-Phenanthrenol, 4*a*-[[3-(dimethylamino)phenyl)methyl]-1,2,3,4,4*a*,9,10,10*a*-octahydro-7-(2-hydroxyethoxy)-2-(1-propynyl)-, [2*R*-(2*α*,4*α*,10*aβ*)]-; See also Example 60.

Examples 697-699

The title compounds of Examples 697-699 were prepared by procedures analogous to those described above in Example 9.

Example 697 2,7-Phenanthrenediol, 1,2,3,4,4*a*,9,10,10*a*-octahydro-1,1,4*a*-trimethyl-2-(1-propynyl)-, MS: 299 (M+1)⁺.

Example 698 2,7-Phenanthrenediol, 2-(3-fluoro-3-methyl-1-butenyl)-1,2,3,4,4*a*,9,10,10*a*-octahydro-4*a*-(phenylmethyl)-, [2*R*-(2*α*,4*α*,10*aβ*)]-, MS: 394 (M+1)⁺.

Example 699 2,7-Phenanthrenediol, 2-(3-fluoro-3-methyl-1-butenyl)-1,2,3,4,4*a*,9,10,10*a*-octahydro-4*a*-(phenylmethyl)-, [2*S*-(2*α*,4*aβ*,10*aα*)]-, MS: 394 (M+1)⁺.

Example 700 2-Phenanthrenol, 2-(3,3-dimethylbutyl)-1,2,3,4,4*a*,9,10,10*a*-octahydro-4*a*-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2*α*,4*α*,10*aβ*)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 485 (M+1)⁺.

Example 701 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(2-phenylethyl)-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 10. MS: 414 (M+1)⁺

Example 702 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-[(methylthio)methyl]-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 81. MS: 370 (M+1)⁺.

Examples 703-705

The title compounds of Examples 703-705 were prepared by procedures analogous to those described above in Example 76.

Example 703 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(2-phenylethyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-, MS: 505 (M+1)⁺.

Example 704 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-5-thiazolyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-, MS: 463 (M+1)⁺.

Example 705 2-Phenanthrenol, 7-[[5-(1,1-dimethylethyl)-1,2,4-oxadiazol-3-yl]methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-, MS: 490 (M+1)⁺.

Example 706 2-Phenanthrenol, 7-[[5-(3,5-dimethyl-4-isoxazolyl)-1,2,4-oxadiazol-3-yl]methoxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 69. MS: 529 (M+1)⁺.

Example 707 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(3-methoxy-1-propynyl)-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 469 (M+1)⁺.

Examples 708-710

The title compounds of Examples 708-710 were prepared by procedures analogous to those described above in Example 81.

- Example 708 2-Phenanthrenol, 2-[(cyclopropylmethoxy)methyl]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-, MS: 485 (M+1)⁺.
- Example 709 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-[(2,2,2-trifluoroethoxy)methyl]-, [2*R*-(2 α ,4 α ,10 α β)]-, MS: 513 (M+1)⁺.
- Example 710 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-[(1-methylethoxy)methyl]-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-, MS: 458 (M+1)⁺.
- Example 711 2-Phenanthrenol, 2-(azidomethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 82. MS: 473 (M+1)⁺.

Examples 712-717

The title compounds of Examples 712-717 were prepared by procedures analogous to those described above in Example 81.

- Example 712 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-[(2-pyridinylmethoxy)methyl]-, [2*R*-(2 α ,4 α ,10 α β)]-, MS: 522 (M+1)⁺.
- Example 713 Propanenitrile, 3-[[1,2,3,4,4a,9,10,10a-octahydro-2-hydroxy-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-phenanthrenyl]methoxy]-, [2*R*-(2 α ,4 α ,10 α β)]-, MS: 484 (M+1)⁺.
- Example 714 2-Phenanthrenol, 2-[(cyclopentyloxy)methyl]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-, MS: 499 (M+1)⁺.
- Example 715 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-[[[3-methyl-3-oxetanyl]methoxy]methyl]-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-, MS: 515 (M+1)⁺.

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Example 716 2-Phenanthrenol, 2-[(1,1-dimethylethoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-, MS: 487 (M+1)⁺.

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Example 717 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-
5 (phenoxymethyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-,
[2*R*-(2 α ,4 α ,10 α β)]-, MS: 507 (M+1)⁺.

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Example 718 1*H*-Benz[*e*]indene-2-carboxylic acid, 2,3,3a,4,5,9b-hexahydro-
9b-(phenylmethyl)-7-(3-pyridinylmethoxy)-, methyl ester, [2*R*-
(2 α ,3 α ,9b β)]-

10 The title compound of this example was prepared by procedures analogous to
those described above in Example 76. MS: 429 (M+1)⁺.

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Example 719 Spiro[1,3-dioxolane-2,2'(1'*H*)-phenanthren]-7'-ol,
3',4',4'a,9',10',10'a-hexahydro-4'a-(phenylmethyl)-, (4'a*S*-
trans)-

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15 The title compound of this example was prepared by procedures analogous to
those described above in Example 7. MS: 351 (M+1)⁺.

Example 720 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-(1*H*-
imidazol-1-ylmethyl)-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α β)]-

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20 The title compound of this example was prepared by procedures analogous to
those described above in Example 48. MS: 390 (M+1)⁺.

Example 721 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
(phenylmethyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-, [2*R*-
(2 α ,4 α ,10 α β)]-; See also Example 48.

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Example 722 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
25 (phenylmethyl)-2-[2-(2-pyridinyl)ethyl]-, [2*S*-(2 α ,4 α ,10 α β)]-

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The title compound of this example was prepared by procedures analogous to
those described above in Example 10. MS: 415 (M+1)⁺.

Examples 723-724

30 The title compounds of Examples 723-724 were prepared by procedures
analogous to those described above in Example 76. MS: 506 (M+1)⁺.

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Example 723 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
(phenylmethyl)-2-[2-(2-pyridinyl)ethyl]-7-(3-pyridinylmethoxy)-,
[2*S*-(2 α ,4 α ,10 α β)]-

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Example 724 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-
[(methylthio)methyl]-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-,
[2*R*-(2 α ,4 α ,10 α)]-, MS: 461 (M+1)⁺.

Example 725 2-Phenanthrenol, 2-[(cyclobutyloxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-

To a solution of 20 mg of the title compound of Preparation 20 and 6 mg of
Na in 1 mL of anhydrous DMF was added 0.019 mL of cyclobutanol at 85 °C under
N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted
with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to
dryness. Purification by preparative TLC SiO₂ using 8% acetone in methylene
chloride as the eluant afforded 18 mg (76%) of the title product of this example as
white fluffy powder. Mass: 484 (M+1)⁺.

Examples 726-734

The title compounds of Examples 726-734 were prepared by procedures
analogous to those described above in Example 725.

Example 726 2-Phenanthrenol, 2-[(2-fluoroethoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 477 (M+1)⁺.

Example 727 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-[[2-
(methylthio)ethoxy)methyl]-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 505 (M+1)⁺.

Example 728 2-Phenanthrenol, 2-[(2,2-dimethylpropoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 501 (M+1)⁺.

Example 729 2-Phenanthrenol, 2-[(2-ethylbutoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 515 (M+1)⁺.

Example 730 2-Phenanthrenol, 2-[(2-butyloxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-, MS: 483 (M+1)⁺.

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Example 731 2-Phenanthrenol, 2-[(cyclohexylmethoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 527 (M+1)⁺.

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Example 732 2-Phenanthrenol, 2-[(cyclopentylmethoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 513 (M+1)⁺.

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Example 733 2-Phenanthrenol, 2-[(cyclobutylmethoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 499 (M+1)⁺.

10 Example 734

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2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
(phenylmethyl)-2-[[[(3-phenyl-1-propynyl)oxy]methyl]-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 545 (M+1)⁺.

Example 735 2-Phenanthrenol, 2-(3-fluoro-3-methyl-1-butynyl)-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-
pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-

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The title compound of this example was prepared by procedures analogous to
those described above in Example 9. MS: 485 (M+1)⁺.

Examples 736-738

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The title compounds of Examples 736-738 were prepared by procedures
analogous to those described above in Example 76.

Example 736 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-(1*H*-
imidazol-1-ylmethyl)-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-
, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 481 (M+1)⁺.

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Example 737 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
(phenylmethyl)-7-(3-pyridinylmethoxy)-2-(1*H*-1,2,4-triazol-1-
ylmethyl)-, [2*R*-(2 α ,4 α ,10 $\alpha\beta$)]-, MS: 482 (M+1)⁺.

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Example 738 Pyridine, 3-[[[3',4',4'a,9',10',10'a-hexahydro-4'a-
(phenylmethyl)spiro[1,3-dioxolane-2,2'(1'*H*)-phenanthren]-7'-
yl]oxy]methyl]-, (4'a*S-trans*)-, MS: 443 (M+1)⁺.

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30 Example 739

2-Phenanthrenol, 2-(ethoxymethyl)-1,2,3,4,4a,9,10,10a-
octahydro-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-, [2*R*-
(2 α ,4 α ,10 $\alpha\beta$)]-

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To a solution of 20 mg of the title compound of Example 676 and 5 mg of 60% NaH in 2 mL of anhydrous DMF was added 11 mg of 2-picolyi chloride hydrochloride at RT under N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC (SiO₂) using 45% EtOAc in hexanes as the eluant afforded 24 mg (96%) of the title product of this example as white fluffy powder. Mass: 458 (M+1)⁺.

Example 740 2-Phenanthrenol, 2-(ethoxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-7-[(5-methyl-3-isoxazolyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2α,4α,10αβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 81. MS: 463 (M+1)⁺.

Example 741 2-Phenanthrenol, 2-(ethoxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-7-[2-(4-morpholinyl)ethoxy]-4a-(phenylmethyl)-, [2*R*-(2α,4α,10αβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 67. MS: 481 (M+1)⁺.

Examples 742-744

The title compounds of Examples 742-744 were prepared by procedures analogous to those described above in Example 74.

Example 742 2-Phenanthrenol, 2-(ethoxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(pyrazinyloxy)-, [2*R*-(2α,4α,10αβ)]-, MS: 446 (M+1)⁺.

Example 743 2-Phenanthrenol, 7-[(2-amino-6-methyl-4-pyrimidinyl)oxy]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-, [2*R*-(2α,4α,10αβ)]-, MS: 475 (M+1)⁺.

Example 744 3-Pyridinecarboxamide, 6-[[7-(ethoxymethyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-2-phenanthrenyl]oxy]-, [4b*S*-(4bα,7α,8αβ)]-, MS: 488 (M+1)⁺.

Example 745 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-[(methylsulfonyl)methyl]-4a-(phenylmethyl)-, [2*R*-(2α,4α,10αβ)]-

At room temperature, under nitrogen, meta-chloroperoxybenzoic acid (58 mg) was added to the title product of Example 702 (20 mg) in CH₂Cl₂ and monitored by TLC. When no starting material remained, the reaction was quenched with 10% sodium bisulfite solution and extracted with CH₂Cl₂ (3X). The organics were combined and dried with Na₂SO₄, filtered and concentrated. Purification by flash chromatography with 10% MeOH in CH₂Cl₂ yielded 15 mg of white solid. Mass: 402 (M+1)⁺.

Example 746 2-Phenanthrenol, 2-(cyclopropylethynyl)-1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound was obtained as described in Example 764 except the title compound of Example 150 was used as starting material. Mass: 478 (M+1)⁺.

Examples 747-748

The title compounds of Examples 747-748 were prepared by procedures analogous to those described above in Example 76.

Example 747 2-Phenanthrenol, 2-(cyclopropylethynyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-, MS: 465 (M+1)⁺.

Example 748 2-Phenanthrenol, 2-(2-cyclopropylethyl)-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-, MS: 469 (M+1)⁺.

Example 749 2-Phenanthrenol, 2-(2-cyclopropylethyl)-1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound was obtained as described in Example 764 except the title product of Example 377 was used as starting material. MS: 482 (M+1)⁺.

Example 749a 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(trifluoromethyl)-, (2*R*,4a*S*,10a*R*)-

The title compound was obtained as described in Example 764 except the title product of Example 799 was used as starting material. MS: 482 (M+1)⁺.

Example 749b 2-Pyridinecarbonitrile, 3-[[[(4b*S*,7*R*,8a*R*)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-4b-(phenylmethyl)-2-phenanthrenyl]oxy]methyl]-

To a solution of 222 mg of the title compound of Example 750 and 55 mg of 60% NaH in 5 mL of anhydrous DMF was added 400 mg of 2-cyanol-3-picolyl chloride hydrochloride at RT under N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by column chromatography using 35% EtOAc in hexanes as the eluant afforded 220 mg (74%) of the title product of this example as white fluffy powder. MS: 439 (M+1)⁺.

Example 750 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-methyl-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 323 (M+1)⁺.

Example 751 2-Phenanthrenol, 2-[(cyclobutyloxy)methyl]-1,2,3,4,4a,9,10,10a-octahydro-7-[(1-oxido-3-pyridinyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 503 (M+1)⁺.

Example 752 Carbamic acid, dimethyl-, 7-(ethoxymethyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-2-phenanthrenyl ester, [4b*S*-(4bα,7α,8aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 58. MS: 439 (M+1)⁺.

Example 753 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-(1-methylethoxy)-4a-(phenylmethyl)-2-[(2-pyridinylmethoxy)methyl]-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 81. MS: 473 (M+1)⁺.

Example 754 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-[[2-(1*H*-pyrazol-1-yl)ethoxy]methyl]-7-(3-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 725. MS: 525 (M+1)⁺.

Example 755 2-Phenanthrenecarboxylic acid, 7-(cyclopropylethynyl)-
4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-,
methyl ester, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to
those described above in Example 14. MS: 416 (M+1)⁺.

Example 756 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-
3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(3,3,3-
trifluoropropyl)-, [2S-(2 α ,4a α ,10a β)]-

The title compound was obtained as described in Example 764 except the title
product of Example 348 was used as starting material. MS: 510 (M+1)⁺.

Example 757 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-
(phenylmethyl)-7-(2-pyridinylmethoxy)-2-(3,3,3-trifluoropropyl)-,
[2S-(2 α ,4a α ,10a β)]-

The title compound of this example was prepared by procedures analogous to
those described above in Example 76. MS: 497 (M+1)⁺.

Example 758 2-Phenanthrenemethanol, 7-(cyclopropylethynyl)-
4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy- α,α -dimethyl-4b-
(phenylmethyl)-, [4bS-(4b α ,7 α ,8a β)]-

The title compound of this example was prepared by procedures analogous to
those described above in Example 19. MS: 415 (M+1)⁺.

Examples 759-760

The title compounds of Examples 759-760 were prepared by procedures
analogous to those described above in Example 725.

Example 759 2-Phenanthrenol, 2-[(cyclopropylmethoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-4-
thiazolyl)methoxy]-4a-(phenylmethyl)-, [2R-(2 α ,4a α ,10a β)]-,
MS: 505 (M+1)⁺.

Example 760 2-Phenanthrenol, 2-[(cyclopropylmethoxy)methyl]-
1,2,3,4,4a,9,10,10a-octahydro-7-[(5-methyl-3-
isoxazolyl)methoxy]-4a-(phenylmethyl)-, [2R-(2 α ,4a α ,10a β)]-,
MS: 489 (M+1)⁺.

Example 761 2-Phenanthrenol, 2-(ethoxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-4-thiazolyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 81. MS: 479 (M+1)⁺.

Example 762 2-Phenanthrenol, 2-[(cyclopropylmethoxy)methyl]-1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 725. MS: 485 (M+1)⁺.

Example 763 2-Phenanthrenol, 2-[(cyclopropylmethoxy)methyl]-1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound was obtained as described in Example 764 except the title product of Example 675 was used as starting material. MS: 498 (M+1)⁺.

Example 764 2-Phenanthrenol, 2-(ethoxymethyl)-1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α β)]-

To a solution of 20 mg of the title compound of Example 676 and 3 mg of 60% NaH in 2 mL of anhydrous DMF was added 9 mg of 2-methyl-3-picolyl chloride hydrochloride at RT under N₂ atmosphere with stirring overnight. The reaction was quenched with NH₄Cl(sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by preparative TLC (SiO₂) using 55% EtOAc in hexanes as the eluant afforded 21 mg (81%) of the title product of this example as white fluffy powder. MS: 472 (M+1)⁺.

Example 765 2-Phenanthrenecarboxamide, 7-(ethoxymethyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-*N*-3-pyridinyl-, [4b*S*-(4b α ,7 α ,8 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. MS: 472 (M+1)⁺.

Example 766 2-Phenanthrenol, 2-(2-cyclopropylethyl)-1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methylphenyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10 α β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 482 (M+1)⁺.

Example 767 2-Phenanthrenol, 2-(2-cyclopropylethyl)-1,2,3,4,4a,9,10,10a-octahydro-7-(phenylmethoxy)-4a-(phenylmethyl)-, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 10. MS: 468 (M+1)⁺.

Example 768 2-Phenanthrenecarbonitrile, 7-(ethoxymethyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-, [4b*S*-(4bα,7α,8aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 81. MS: 377 (M+1)⁺.

Examples 769-770

The title compounds of Examples 769-770 were prepared by procedures analogous to those described above in Example 725.

Example 769 2-Phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-[(2,2,2-trifluoroethoxy)methyl]-, [4b*S*-(4bα,7α,8aβ)]-, MS: 430 (M+1)⁺.

Example 770 2-Phenanthrenecarbonitrile, 7-[(cyclopropylmethoxy)methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-, [4b*S*-(4bα,7α,8aβ)]-, MS: 403 (M+1)⁺.

Example 771 2-Phenanthrenecarboxamide, 7-(2-pentyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, [4b*S*-(4bα,7α,8aβ)]-

To a stirring solution of 150 mg of 2-phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(pentyl)-, methyl ester, [4b*S*-(4bα,7α,8aβ)]- in 7 mL of dichloromethane was added 2 mL of 0.5 M 2-methyl-3-aminomethylpyridine aluminum amide solution prepared as in Example 772. The mixture was heated to reflux for 3 h. An additional 1 mL of 0.5 M 2-methyl-3-aminomethylpyridine aluminum amide solution was added and the mixture was heated to reflux for an additional 2 h. The mixture was cooled to 0 °C. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over

Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 10% MeOH in dichloromethane as the eluant afforded 172 mg (94 %) of the title product of this example as a white solid. MS: 511 (M+1)⁺.

Example 771A-1 2 (2-Phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(butyl)-, methyl ester, [4bS-(4b α ,7 α ,8a β)]-;

The title compound of this example was prepared by procedures analogous to those described above in Example 14. MS: 421 (M+1)⁺.

Example 771A-2 2-Phenanthrenecarboxamide, 7-butyl-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR)-

To a stirring solution of 210 mg of the title compound of Example 771A-1 in 10 mL of dichloromethane was added 3 mL of 0.5 M 2-methyl-3-aminomethylpyridine aluminum amide solution prepared as in Example 772. The mixture was heated to reflux overnight. The mixture was cooled to 0 °C. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 40% acetone in hexanes to 50% acetone in hexanes as the gradient eluant afforded 163 mg (63%) of the title product of this example as a white solid. MS: 497 (M+1)⁺.

Example 771B 2-Phenanthrenecarboxamide, 7-(cyclopropylethynyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR)- (Refer to Scheme C: C-5 → C-8)

To a stirring solution of 200 mg of 2-phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(cyclopropylethynyl)-, methyl ester, [4bS-(4b α ,7 α ,8a β)]- in 10 mL of dichloromethane was added 3 mL of 0.5 M 2-methyl-3-aminomethylpyridine aluminum amide solution prepared as in Example 772. The mixture was heated to reflux overnight. The mixture was cooled to 0 °C. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 40% acetone in hexanes to 50% acetone in hexanes as the gradient

eluant afforded 196 mg (81%) of the title product of this example as a white solid.

MS: 505 (M+1)⁺.

Example 771C-1 Methanesulfonic acid, trifluoro, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-2-phenanthrenylester, [4bS, 7S, 8aR]-

The title compound of this example was prepared by procedures analogous to those described above for the preparation of the title compound of Example 13. MS: 537 (M+1)⁺; ¹H NMR (400MHz, d₆-acetone) δ 7.18 (d, 1H, J = 2.9) 6.83 (dd, 1H, J = 2.9, 8.7), 6.43 (d, 1H, J = 8.7).

Example 771C-2 2-Phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-, methyl ester, [4bS, 7S, 8aR]-

The title compound of this example was prepared by procedures analogous to those described above for the preparation of the title compound of Example 14. MS: 447 ((M+1)⁺; ¹H NMR (400 Mhz, CDOD₃) δ 7.75 (d, 1H, J = 1.7), 7.40 (dd, 1H, J = 1.7, 8.2), 6.39 (d, 1H, J = 8.2).

Example 771C-3 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-, (4bS,7S,8aR)-

To a stirring solution of 286 mg of the title compound of Example 771C-2 in 12 mL of dichloromethane was added 4 mL of 0.5 M 2-methyl-3-aminomethylpyridine aluminum amide solution prepared as in Example 772. The mixture was heated to reflux overnight. The mixture was cooled to 0°C. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 40% acetone in hexanes to 50% acetone in hexanes as the gradient eluant afforded 272 mg (79%) of the title product of this example as a white solid. MS: 537 (M+1)⁺.

Example 771D 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(propoxymethyl)-N-3-pyridinyl-, (4bS,7R,8aR)-

To a stirring solution of 50 mg of 2-phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(propoxymethyl)-, methyl ester, [4bS-(4bα,7α,8aβ)]- in 5 mL of dichloromethane was added 4 mL of 0.5

M 3-aminopyridine aluminum amide solution prepared as in Example 772. The mixture was heated to reflux overnight. The mixture was cooled to 0 °C. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by preparative TLC (SiO₂) with 3 % MeOH in dichloromethane afforded 9 mg (16%) of the title product of this example as a white solid. MS: 485 (M+1)⁺.

Example 771E-1 (2-Phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(methyl)-, methyl ester, [4bS-(4b α ,7 α ,8a β)]-)

The title compound of this example was prepared by procedures analogous to those described above in Example 14. ¹HNMR (400MHz, CD₃OD) δ 7.81 (s,1H), 3.90 (s, 1H), 1.29 (s, 1H); MS: 365 (M+1)⁺.

Example 771E-2 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR)-

To a stirring solution of 300 mg of the title compound of Example 771E-1 in 16 mL of dichloromethane was added 8.2 mL of 0.5 M 2-methyl-3-aminomethylpyridine aluminum amide solution prepared as in Example 772. The mixture was heated to reflux overnight. The mixture was cooled to 0 °C. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 40% acetone in hexanes to 50% acetone in hexanes as the gradient eluant afforded 344 mg (92%) of the title product of this example as a white solid. MS: 455 (M+1)⁺.

Example 772 2-Phenanthrenecarboxamide, 7-(ethoxymethyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-8a-methyl-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-,[4bS-(4b α ,7 α ,8a β)]-

To a stirring solution of 31 mL of 2.0 M trimethylaluminum in toluene and 24 mL of dichloromethane was added 8.25 g of 2-methyl-3-aminomethylpyridine in 80 mL of dichloromethane at 0 °C under N₂. The mixture was stirred at 0 °C for 20 min.

then at RT for 1 h to give 2-methyl-3-aminomethylpyridine aluminum amide solution. A separate flask was charged with 1.68 g of 2-phenanthrenecarboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(ethoxymethyl)-, methyl ester, [4bS-(4b α ,7 α ,8a β)]- in 80 mL of dichloromethane. To this solution was added 32 mL of 2-methyl-3-aminomethylpyridine aluminum amide solution, prepared as described above. The mixture was heated to reflux overnight. The mixture was cooled to 0 °C. To the reaction mixture was added 1N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with dichloromethane, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 40% acetone in hexanes to 50% acetone in hexanes as the gradient eluant afforded 1.9 g (96 %) of the title product of this example as a white solid. MS: 499 (M+1)⁺.

Example 773 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-[(1-methylethoxy)methyl]-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-, [2*R*-(2 α ,4 α ,10a β)]-

To a solution of 500 mg of the title product of Preparation 21 and 135 mg of Na in 5 mL of anhydrous DMF was added 10 ml of isopropanol at 85 °C under N₂ atmosphere overnight. The reaction was quenched with NH₄Cl (sat.), extracted with EtOAc (X3), washed with brine, dried over Na₂SO₄, filtered and concentrated to dryness. Purification by column chromatography using 1.5% methanol in methylene chloride as the eluant afforded 528 mg (93%) of the title product of this example as white fluffy powder. MS: 486 (M+1)⁺

Example 774 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-[(2,2,2-trifluoroethoxy)methyl]-, [2*R*-(2 α ,4 α ,10a β)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 773. MS: 525.6 (M+1)⁺.

Example 775 2(3*H*)-Phenanthrenone, 4a-[(4-isopropylaminophenyl)methyl]-4,4a,9,10-tetrahydro-7-hydroxy-, (*S*)-; MS: 362 (M+H)⁺; see also Preparation 4.

Example 776 2,7-Phenanthrenediol, 4a-[(4-aminophenyl)methyl]-1,2,3,4,4a,9,10,10a-octahydro-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10a β)]-;

5 The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 462 (M+1)⁺.

10 Example 777 2-Phenanthrenol, 7-[(2-chloro-4-pyrimidinyl)oxy]-
1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-
5 propynyl)-, [2*R*-(2α,4α,10αβ)]-

15 The title compound of this example was prepared by procedures analogous to those described above in Example 74. MS: 460 (M+1)⁺.

Example 778 3*H*-Naphtho[2,1-*b*]pyran-3-one, 1,2,4a,5,6,10b-hexahydro-8-
hydroxy-10b-(phenylmethyl)-

10 The title compound of this example was prepared by procedures analogous to those described above in Example 3. MS: 309 (M+1)⁺.

20 Example 779 1*H*-Naphtho[2,1-*b*]pyran-3,8-diol, 2,3,4a,5,6,10b-hexahydro-
10b-(phenylmethyl)-3-(1-propynyl)-

25 The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 349 (M+1)⁺.

Example 780 1*H*-Naphtho[2,1-*b*]pyran-8-ol, 2,3,4a,5,6,10b-hexahydro-10b-
(phenylmethyl)-3-[(phenylmethyl)imino]-, (4a*S*,10b*R*)-

30 The title compound of this example was prepared by procedures analogous to those described above in Example 77. MS: 397 (M+1)⁺.

20 Example 781 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-
(methoxymethyl)-4a-(phenylmethyl)-, (2*S*,4a*S*,10a*R*)-

35 The title compound of this example was prepared by procedures analogous to those described above in Example 81. MS: 353 (M+1)⁺.

25 Example 782 Benzonitrile, 4-[(2*R*,4a*S*)-3,4,9,10-tetrahydro-2,7-dihydroxy-2-
(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]-

40 The title compound of this example was prepared by procedures analogous to those described above in Example 5. MS: 370 (M+1)⁺.

45 Example 783 2-Phenanthrenecarbonitrile, 4b-[(4-cyanophenyl)methyl]-
4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(1-propynyl)-,
30 (4b*S*,7*R*,8a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 381 (M+1)⁺.

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Example 784 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(propoxymethyl)-, (4b*S*,7*R*,8a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. MS: 514 (M+1)⁺.

Example 785 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-2-(1-pentynyl)-4a-(phenylmethyl)-, (2*R*,4a*S*,10a*R*)-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 481 (M+1)⁺.

Examples 786-793

The title compounds of Examples 786-793 were prepared by procedures analogous to those described above in Example 244.

Example 786 2-Phenanthrenecarboxamide, 7-(1-butyryl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4b*S*,7*R*,8a*R*)-; MS: 494 (M+1)⁺.

Example 787 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-[(2,2,2-trifluoroethoxy)methyl]-, (4b*S*,7*R*,8a*R*)-; MS: 554 (M+1)⁺.

Example 788 2-Phenanthrenecarboxamide, 7-[(cyclopropylmethoxy)methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4b*S*,7*R*,8a*R*)-; MS: 526 (M+1)⁺.

Example 789 2-Phenanthrenecarboxamide, 7-[(cyclopropylmethoxy)methyl]-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-*N*-3-pyridinyl-, (4b*S*,7*R*,8a*R*)-; MS: 498 (M+1)⁺.

Example 790 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-[(1-methylethoxy)methyl]-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4b*S*,7*R*,8a*R*)-; MS: 514 (M+1)⁺.

Example 791 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-4b-(phenylmethyl)-*N*-3-pyridinyl-, (4b*S*,7*R*,8a*R*)- MS: 428 (M+1)⁺.

Example 792 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(3-methylbutyl)-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR)-; MS: 512 (M+1)⁺.

Example 793 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-(3-methyl-1-butyryl)-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR)-; MS: 508 (M+1)⁺.

Example 794 2-Phenanthrenol, 2-(1-butyryl)-1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-, (2R,4aS,10aR)-

The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 467 (M+1)⁺.

Example 795 2-Phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-[(2-methylpropoxy)methyl]-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aS)-

The title compound of this example was prepared by procedures analogous to those described above in Example 81. MS: 528 (M+1)⁺.

Examples 796-798

The title compounds of Examples 796-798 were prepared by procedures analogous to those described above in Example 9.

Example 796 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-methyl-4a-(phenylmethyl)-, (2R,4aS,10aS)-; MS: 323 (M+1)⁺.

Example 797 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-methyl-4a-(phenylmethyl)-, (2S,4aS,10aS)-; MS: 323 (M+1)⁺.

Example 798 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-2-methyl-4a-propyl-, (2R,4aR,10aS)-; MS: 275 (M+1)⁺.

Example 799 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(trifluoromethyl)-, (2R,4aS,10aR)-;

To a solution of 455 mg of the title product of Example 6 in 20 mL of anhydrous THF and 15 mL of 1 M trifluoromethyl trimethylsilane was added 194 mg of TBAF at 0 °C under nitrogen atmosphere for 10 min. The mixture was then stirred at RT for 3 hr. Two equivalents of TBAF were added and stirred for 1 hr at RT. The mixture was concentrated and purification by flash chromatography SiO₂ using 100%

hexanes to 20% ethyl acetate in hexanes as the gradient eluant afforded 518 mg (93%) of the title product as white fluffy powder. MS m/z 375 (M+1)⁺.

Example 800 2,7-Phenanthrenediol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(trifluoromethyl)-, (4aS,10aS)-

5 The title compound of this example was prepared by procedures analogous to those described above in Example 799. MS: 377 (M+1)⁺.

15 Example 801 2-Phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-2-methyl-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-, (2R,4aS,10aS)-

10 The title compound of this example was prepared by procedures analogous to those described above in Example 76. MS: 429 (M+1)⁺.

20 Example 802 2-Phenanthrenecarboxamide, 7-(ethoxymino)-4b,5,6,7,8,8a,9,10-octahydro-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7Z,8aR)-

25 15 The title compound of this example was prepared by procedures analogous to those described above in Example 244. MS: 483 (M+1)⁺.

Example 803A Methanesulfonic acid, trifluoro, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b (phenylmethyl)-7-(trifluoromethyl)-2-phenathrenyl ester [(4b α , 7 α , 8a β)]

20 A solution of 50 mg of the title compound of Example 799, 55 mg of K₂CO₃, 43 mg of 4-nitrophenyltriflate in 5 mL of anhydrous DMF was stirred under N₂ at room temperature overnight. The reaction mixture was quenched with NaHCO₃ (sat.), extracted with EtOAc, dried over MgSO₄, filtered and concentrated to dryness. Purification by preparative TLC using 25% EtOAc in hexanes as the eluant yielded 45

25 mg (66%) of the title product of this example as a white solid. MS: 509 (M+1)⁺

40 Example 803B 2-Phenanthrene carboxylic acid, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b(phenylmethyl)-7-(trifluoromethyl)-, methyl ester, [4bS-(4b α , 7 α , 8a β)]

Starting with the title product of Example 803A and utilizing procedures analogous to those described in Example 14, the title product of this example was obtained. MS: 419 ((M+1).⁺

45 30 Example 803C 2-Phenanthrenecarboxamide, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(trifluoromethyl)-, (4bS, 7R, 8aR)-

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To a stirring solution of 300 mg of the title compound of Example 803B in 12 mL of dichloromethane was added 4 mL of 0.5 M 2-methyl-3-aminomethylpyridine aluminum amide solution prepared as in Example 772. The mixture was heated to reflux overnight. The mixture was cooled to 0 °C. To the reaction mixture was added 1 N HCl dropwise until the aqueous layer was approximately pH 4. The resultant mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and concentrated to dryness. Purification by flash chromatography over SiO₂ using 40% acetone in hexanes to 50% acetone in hexanes as the gradient eluant afforded 290 mg (80%) of the title product of this example as a white solid. MS: 509 (M+1)⁺.

Example 804 2-Phenanthrenecarboxamide, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-7-methyl-N-[(2-methyl-3-pyridinyl)methyl]-4b-propyl-, (4bR, 7R, 8aS)-

The title compound of this example was prepared by procedures analogous to those described above in Example 244. MS: 408 (M+1)⁺.

Example 805 2(3*H*)-Phenanthrenone, 4a-(2-butenyl)-4,4a,9,10-tetrahydro-7-methoxy-, [*S*-(*E*)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 1. MS: 283 (M+1)⁺.

Example 806 Carbamic acid, [4-[[1,3,4,9,10,10a-hexahydro-2,7-dihydroxy-2-(1-propynyl)-4a(2*H*)-phenanthrenyl]methyl]phenyl]-, 1,1-dimethylethyl ester, [2*R*-(2α,4α,10aβ)]-

The title compound of this example was prepared by procedures analogous to those described above in Example 9. MS: 463 (M+1)⁺

The compounds of this invention either alone or in combination with each other or other compounds generally will be administered in a convenient formulation. The following formulation examples only are illustrative and are not intended to limit the scope of the present invention.

In the formulations which follow, "active ingredient" means a compound of this invention.

Formulation 1: Gelatin Capsules

Hard gelatin capsules are prepared using the following:

Ingredient	Quantity (mg/capsule)
Active ingredient	0.25-100
Starch, NF	0-850
Starch flowable powder	0-50
Silicone fluid 350 centistokes	0-15

A tablet formulation is prepared using the ingredients below:

Formulation 2: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Cellulose, microcrystalline	200-650
Silicon dioxide, fumed	10-650
Stearic acid	5-15

The components are blended and compressed to form tablets.

Alternatively, tablets each containing 0.25-100 mg of active ingredients are made up as follows:

Formulation 3: Tablets

Ingredient	Quantity (mg/tablet)
Active ingredient	0.25-100
Starch	45
Cellulose, microcrystalline	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl cellulose	4.5
Magnesium stearate	0.5
Talc	1

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50° - 60°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc,

previously passed through a No. 60 U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets.

Suspensions each containing 0.25-100 mg of active ingredient per 5 ml dose are made as follows:

5 Formulation 4: Suspensions

Ingredient	Quantity (mg/5 ml)
Active ingredient	0.25-100 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 mg
Benzoic acid solution	0.10 mL
Flavor	q.v.
Color	q.v.
Purified Water to	5 mL

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form smooth paste. The benzoic acid solution, flavor, and color are diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume. An aerosol solution is prepared containing the following ingredients:

10 Formulation 5: Aerosol

Ingredient	Quantity (% by weight)
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00

The active ingredient is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to 30°C, and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remaining propellant. The valve units are then fitted to the container.

Suppositories are prepared as follows:

15 Formulation 6: Suppositories

Ingredient	Quantity (mg/suppository)
Active ingredient	250
Saturated fatty acid glycerides	2,000

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The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum necessary heat. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

5 An intravenous formulation is prepared as follows:

Formulation 7: Intravenous Solution

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Ingredient	Quantity
Active ingredient	20 mg
Isotonic saline	1,000 mL

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The solution of the above ingredients is intravenously administered to a patient at a rate of about 1 mL per minute.

10 The active ingredient in any of the formulations above may also be a combination of agents.

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Claims

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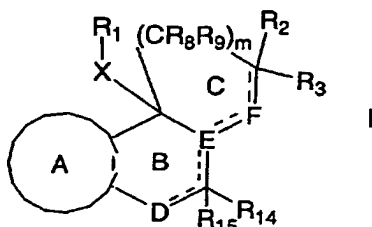
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CLAIMS

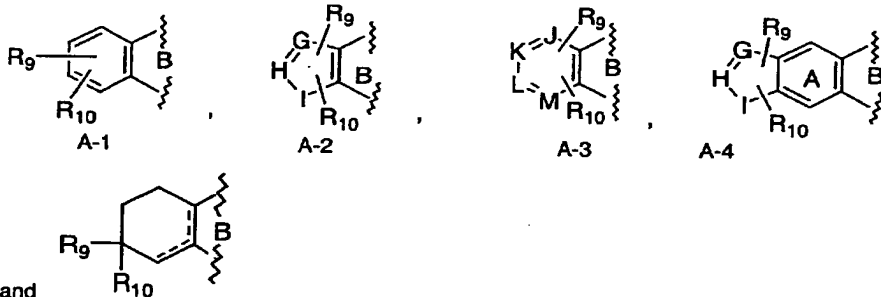
1. A compound of formula I



an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; wherein m is 1 or 2;

--- represents an optional bond;

A is selected from the group consisting of



and

A-5

D is CR_7 , CR_7R_{16} , N, NR_7 or O;

E is C, CR_8 or N;

F is CR_4 , CR_4R_5 or O;

G, H and I together with 2 carbon atoms from the A-ring or 2 carbon atoms from the B-ring form a 5-membered heterocyclic ring comprising one or more N, O or S atoms; provided that there is at most one of O and S per ring;

J, K, L and M together with 2 carbon atoms from the B-ring forms a 6-membered heterocyclic ring comprising 1 or more N atoms;

X is a) absent, b) $-\text{CH}_2-$, c) $-\text{CH}(\text{OH})-$ or d) $-\text{C}(\text{O})-$;

- 5 R_1 is a) -H, b) -Z-CF₃, c) -(C₁-C₆)alkyl, d) -(C₂-C₆)alkenyl, e) -(C₂-C₆)alkynyl, f) -CHO, g) -CH=N-OR₁₂, h) -Z-C(O)OR₁₂, i) -Z-C(O)-NR₁₂R₁₃, j) -Z-C(O)-NR₁₂-Z-het, k) -Z-NR₁₂R₁₃, l) -Z-NR₁₂het, m) -Z-het, n) -Z-O-het, o) -Z-aryl', p) -Z-O-aryl', q) -CHOH-aryl' or r) -C(O)-aryl' wherein aryl' in substituents o) to r) is substituted
- 10 independently with 0, 1 or 2 of the following: -Z-OH, -Z-NR₁₂R₁₃, -Z-NR₁₂-het, -C(O)NR₁₂R₁₃, -C(O)O(C₁-C₆)alkyl, -C(O)OH, -C(O)-het, -NR₁₂-C(O)-(C₁-C₆)alkyl, -NR₁₂-C(O)-(C₂-C₆)alkenyl, -NR₁₂-C(O)-(C₂-C₆)alkynyl, -NR₁₂-C(O)-Z-het, -CN, -Z-het, -O-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, -O-(C₁-C₃)alkyl-C(O)O(C₁-C₆)alkyl, -NR₁₂-Z-C(O)O(C₁-C₆)alkyl, -N(Z-C(O)O(C₁-C₆)alkyl)₂, -NR₁₂-Z-C(O)-NR₁₂R₁₃, -Z-NR₁₂-SO₂-R₁₃, -NR₁₂-SO₂-het, -C(O)H, -Z-NR₁₂-Z-O(C₁-C₆)alkyl, -Z-NR₁₂-Z-NR₁₂R₁₃, -Z-NR₁₂-(C₃-C₆)cycloalkyl, -Z-N(Z-O(C₁-C₆)alkyl)₂, -SO₂R₁₂, -SOR₁₂, -SR₁₂, -SO₂NR₁₂R₁₃, -O-C(O)-(C₁-C₄)alkyl, -O-SO₂-(C₁-C₄)alkyl, -halo or -CF₃;
- 15 Z for each occurrence is independently a) -(C₀-C₆)alkyl, b) -(C₂-C₆)alkenyl or c) -(C₂-C₆)alkynyl;
- 20 R_2 is a) -H, b) -halo, c) -OH, d) -(C₁-C₆)alkyl substituted with 0 or 1 -OH, e) -NR₁₂R₁₃, f) -Z-C(O)O(C₁-C₆)alkyl, g) -Z-C(O)NR₁₂R₁₃, h) -O-(C₁-C₆)alkyl, i) -Z-O-C(O)-(C₁-C₆)alkyl, j) -Z-O-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, k) -Z-O-(C₁-C₃)alkyl-C(O)-O(C₁-C₆)alkyl, l) -O-(C₂-C₆)alkenyl, m) -O-(C₂-C₆)alkynyl, n) -O-Z-het, o) -COOH, p) -C(OH)R₁₂R₁₃ or q) -Z-CN;
- 25 R_3 is a) -H, b) -(C₁-C₁₀)alkyl wherein 1 or 2 carbon atoms, other than the connecting carbon atom, may optionally be replaced with 1 or 2 heteroatoms independently selected from S, O and N and wherein each carbon atom is substituted with 0, 1 or 2 R_y, c) -(C₂-C₁₀)alkenyl substituted with 0, 1 or 2 R_y, d) -(C₂-C₁₀)alkynyl wherein 1 carbon atom, other than the connecting carbon atom, may optionally be replaced with 1 oxygen atom and wherein each carbon atom is substituted with 0, 1 or 2 R_y, e) -CH=C=CH₂, f) -CN, g) -(C₃-C₆)cycloalkyl, h) -Z-aryl, i) -Z-het, j) -C(O)O(C₁-C₆)alkyl, k) -O(C₁-C₆)alkyl, l) -Z-S-R₁₂, m) -Z-S(O)-R₁₂, n) -Z-S(O)₂-R₁₂, o) -CF₃ p) -NR₁₂O-(C₁-C₆)alkyl or q) -CH₂OR_y;
- 30 provided that one of R₂ and R₃ is absent when there is a double bond between CR₂R₃ (the 7 position) and the F moiety (the 8 position) of the C-ring;
- 35 R_y for each occurrence is independently a) -OH, b) -halo, c) -Z-CF₃, d) -Z-CF(C₁-C₃ alkyl)₂, e) -CN, f) -NR₁₂R₁₃, g) -(C₃-C₆)cycloalkyl, h) -(C₃-C₆)cycloalkenyl, i) -(C₀-C₃)alkyl-aryl, j) -het or k) -N₃;

or R_2 and R_3 are taken together to form a) $=CHR_{11}$, b) $=NOR_{11}$, c) $=O$, d) $=N-NR_{12}$, e) $=N-NR_{12}-C(O)-R_{12}$, f) oxiranyl or g) 1,3-dioxolan-4-yl;

R_4 and R_5 for each occurrence are independently a) $-H$, b) $-CN$, c) $-(C_1-C_6)$ alkyl substituted with 0 to 3 halo, d) $-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo, e) $-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo, f) $-O-(C_1-C_6)$ alkyl substituted with 0 to 3 halo, g) $-O-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo, h) $-O-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo, i) halo, j) $-OH$, k) (C_3-C_6) cycloalkyl or l) (C_3-C_6) cycloalkenyl;

or R_4 and R_5 are taken together to form $=O$;

R_6 is a) $-H$, b) $-CN$, c) $-(C_1-C_6)$ alkyl substituted with 0 to 3 halo, d) $-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo, e) $-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo or f) $-OH$;

R_7 and R_{16} for each occurrence are independently a) $-H$, b) $-halo$, c) $-CN$, d) $-(C_1-C_6)$ alkyl substituted with 0 to 3 halo, e) $-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo or f) $-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo; provided that R_7 is other than $-CN$ or $-halo$ when D is NR_7 ;

or R_7 and R_{16} are taken together to form $=O$;

R_8 , R_9 , R_{14} and R_{15} for each occurrence are independently a) $-H$, b) $-halo$, c) (C_1-C_6) alkyl substituted with 0 to 3 halo, d) $-(C_2-C_6)$ alkenyl substituted with 0 to 3 halo, e) $-(C_2-C_6)$ alkynyl substituted with 0 to 3 halo, f) $-CN$, g) $-(C_3-C_6)$ cycloalkyl, h) $-(C_3-C_6)$ cycloalkenyl, i) $-OH$, j) $-O-(C_1-C_6)$ alkyl, k) $-O-(C_1-C_6)$ alkenyl, l) $-O-(C_1-C_6)$ alkynyl, m) $-NR_{12}R_{13}$, n) $-C(O)OR_{12}$ or o) $-C(O)NR_{12}R_{13}$;

or R_8 and R_9 are taken together on the C-ring to form $=O$; provided that when m is 2, only one set of R_8 and R_9 are taken together to form $=O$;

or R_{14} and R_{15} are taken together to form $=O$; provided that when R_{14} and R_{15} are taken together to form $=O$, D is other than CR_7 and E is other than C ;

R_{10} is a) $-(C_1-C_{10})$ alkyl substituted with 0 to 3 substituents independently selected from $-halo$, $-OH$ and $-N_3$, b) $-(C_2-C_{10})$ alkenyl substituted with 0 to 3 substituents independently selected from $-halo$, $-OH$ and $-N_3$, c) $-(C_2-C_{10})$ alkynyl substituted with 0 to 3 substituents independently selected from $-halo$, $-OH$ and $-N_3$, d) $-halo$, e) $-Z-CN$, f) $-OH$, g) $-Z-het$, h) $-Z-NR_{12}R_{13}$, i) $-Z-C(O)-het$, j) $-Z-C(O)-(C_1-C_6)$ alkyl, k) $-Z-C(O)-NR_{12}R_{13}$, l) $-Z-C(O)-NR_{12}-Z-CN$, m) $-Z-C(O)-NR_{12}-Z-het$, n) $-Z-C(O)-NR_{12}-Z-aryl$, o) $-Z-C(O)-NR_{12}-Z-NR_{12}R_{13}$, p) $-Z-C(O)-NR_{12}-Z-O(C_1-C_6)$ alkyl, q) $-(C_0-C_6)$ alkyl- $C(O)OH$, r) $-Z-C(O)O(C_1-C_6)$ alkyl, s)

5

-Z-O-(C₀-C₆)alkyl-het, t) -Z-O-(C₀-C₆)alkyl-aryl, u) -Z-O-(C₁-C₆)alkyl substituted with 0 to 2 R_x, v) -Z-O-(C₁-C₆)alkyl-CH(O), w) -Z-O-(C₁-C₆)alkyl-NR₁₂-het, x)
 -Z-O-Z-het-Z-het, y) -Z-O-Z-het-Z-NR₁₂R₁₃, z) -Z-O-Z-het-C(O)-het, a1)
 -Z-O-Z-C(O)-het, b1) -Z-O-Z-C(O)-het-het, c1) -Z-O-Z-C(O)-(C₁-C₆)alkyl, d1)
 5 -Z-O-Z-C(S)-NR₁₂R₁₃, e1) -Z-O-Z-C(O)-NR₁₂R₁₃, f1)
 -Z-O-Z-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, g1) -Z-O-Z-C(O)-O(C₁-C₆)alkyl, h1)
 -Z-O-Z-C(O)-OH, i1) -Z-O-Z-C(O)-NR₁₂-O(C₁-C₆)alkyl, j1) -Z-O-Z-C(O)-NR₁₂-OH, k1)
 -Z-O-Z-C(O)-NR₁₂-Z-NR₁₂R₁₃, l1) -Z-O-Z-C(O)-NR₁₂-Z-het, m1)
 -Z-O-Z-C(O)-NR₁₂-SO₂-(C₁-C₆)alkyl, n1) -Z-O-Z-C(=NR₁₂)(NR₁₂R₁₃), o1)
 10 -Z-O-Z-C(=NOR₁₂)(NR₁₂R₁₃), p1) -Z-NR₁₂-C(O)-O-Z-NR₁₂R₁₃, q1) -Z-S-C(O)-NR₁₂R₁₃,
 r1) -Z-O-SO₂-(C₁-C₆)alkyl, s1) -Z-O-SO₂-aryl, t1) -Z-O-SO₂-NR₁₂R₁₃, u1)
 -Z-O-SO₂-CF₃, v1) -Z-NR₁₂C(O)OR₁₃ or w1) -Z-NR₁₂C(O)R₁₃;

or R₉ and R₁₀ are taken together on the moiety of formula A-5 to form a) = O
 or b) = NOR₁₂;

25

15 R₁₁ is a) -H, b) -(C₁-C₅)alkyl, c) -(C₃-C₆)cycloalkyl or d) -(C₀-C₃)alkyl-aryl;

R₁₂ and R₁₃ for each occurrence are each independently a) -H, b)

-(C₁-C₆)alkyl wherein 1 or 2 carbon atoms, other than the connecting carbon atom,
 may optionally be replaced with 1 or 2 heteroatoms independently selected from S, O
 and N and wherein each carbon atom is substituted with 0 to 6 halo, c)

30

20 -(C₂-C₆)alkenyl substituted with 0 to 6 halo or d) -(C₁-C₆)alkynyl wherein 1 carbon
 atom, other than the connecting carbon atom, may optionally be replaced with 1
 oxygen atom and wherein each carbon atom is substituted with 0 to 6 halo;

35

or R₁₂ and R₁₃ are taken together with N to form het;

or R₆ and R₁₄ or R₁₅ are taken together to form 1,3-dioxolanyl;

25 aryl is a) phenyl substituted with 0 to 3 R_x, b) naphthyl substituted with 0 to 3
 R_x or c) biphenyl substituted with 0 to 3 R_x;

40

het is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring
 containing from one (1) to three (3) heteroatoms independently selected from the
 group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in
 30 which any of the above heterocyclic rings is fused to a benzene ring or another
 heterocycle; and the nitrogen may be in the oxidized state giving the N-oxide form;
 and substituted with 0 to 3 R_x;

45

R_x for each occurrence is independently a) -halo, b) -OH, c) -(C₁-C₆)alkyl, d)

-(C₂-C₆)alkenyl, e) -(C₂-C₆)alkynyl, f) -O(C₁-C₆)alkyl, g) -O(C₂-C₆)alkenyl, h)

50

55

-O(C₂-C₆)alkynyl, i) -(C₀-C₆)alkyl-NR₁₂R₁₃, j) -C(O)-NR₁₂R₁₃, k) -Z-SO₂R₁₂, l) -Z-SOR₁₂,
 m) -Z-SR₁₂, n) -NR₁₂-SO₂R₁₃, o) -NR₁₂-C(O)-R₁₃, p) -NR₁₂-OR₁₃, q) -SO₂-NR₁₂R₁₃,
 r) -CN, s) -CF₃, t) -C(O)(C₁-C₆)alkyl, u) =O, v) -Z-SO₂-phenyl or w) -Z-SO₂-het';

aryl' is phenyl, naphthyl or biphenyl;

het' is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring
 containing from one (1) to three (3) heteroatoms independently selected from the
 group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in
 which any of the above heterocyclic rings is fused to a benzene ring or another
 heterocycle;

provided that:

1) X-R₁ is other than hydrogen or methyl;

2) when R₉ and R₁₀ are substituents on the A-ring, they are other than mono-
 or di-methoxy;

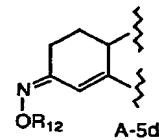
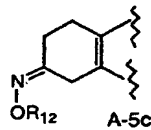
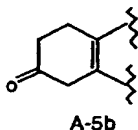
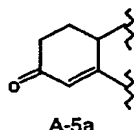
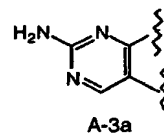
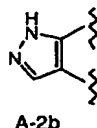
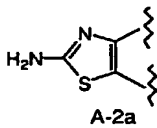
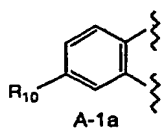
3) when R₂ and R₃ are taken together to form =CHR₁₁ or =O wherein R₁₁ is
 -O(C₁-C₆)alkyl, then -X-R₁ is other than (C₁-C₄)alkyl;

4) when R₂ and R₃ taken together are C=O and R₉ is hydrogen on the A-ring;
 or when R₂ is hydroxy, R₃ is hydrogen and R₉ is hydrogen on the A-ring, then R₁₀ is
 other than -O-(C₁-C₆)alkyl or -O-CH₂-phenyl at the 2-position of the A-ring;

5) when X-R₁ is (C₁-C₄)alkyl, (C₂-C₄)alkenyl or (C₂-C₄)alkynyl, R₉ and R₁₀ are
 other than mono-hydroxy or =O, including the diol form thereof, when taken together;
 and

6) when X is absent, R₁ is other than a moiety containing a heteroatom
 independently selected from N, O or S directly attached to the juncture of the B-ring
 and the C-ring.

2. A compound of claim 1, an isomer thereof, a prodrug of said compound or isomer,
 or a pharmaceutically acceptable salt of said compound, isomer or prodrug; wherein
 the A-ring is selected from the group consisting of:



D is CR₇, CR₁₈R₇ or O;

E is C, CR₆ or N;

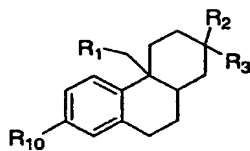
F is CR₄, CR₄R₅ or O; and

X is -CH₂-.

3. A compound of claim 2, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; wherein D is CH₂; E is CH; F is CH₂; R₈ is -H; R₉ is -H; m is 2; R₁₄ is -H; R₁₅ is -H; and the

A-ring is the moiety of formula A-1a.

4. A compound of claim 3 of formula II



an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

wherein R₂ is a) -OH or b) -O-CH₂-het;

R₃ is a) -(C₁-C₆)alkyl substituted with 0 or 1 of the following: -CF₃, -CN,

-(C₃-C₆)cycloalkyl, -phenyl or -N₃, b) -C≡C- substituted with 1 of the following:

-(C₁-C₆)alkyl, -Cl, -CF₃, -(C₃-C₆)cycloalkyl, -phenyl or -benzyl; c) -CH₂OH, d)

-CH₂O(C₁-C₅)alkyl wherein 1 carbon atom may optionally be replaced with 1 oxygen atom, e) -CH₂O(C₂-C₅)alkenyl, f) -CH₂O(C₂-C₅)alkynyl wherein 1 carbon atom may

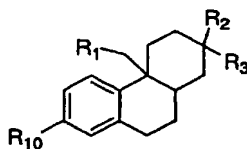
optionally be replaced with 1 oxygen atom, g) -CH₂OR_y, h) -CN or i) -CF₃;

R_y is a) -(C₁-C₃)alkyl -CF₃, b) -(C₃-C₆)cycloalkyl, c) -phenyl or d) -benzyl;

or R₂ and R₃ are taken together to form a) -1,3-dioxolan-4-yl or b) =NOR₁₁;

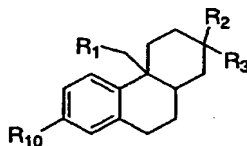
R₁₁ is a) -H, b) -(C₁-C₅)alkyl, c) -(C₃-C₆)cycloalkyl, d) -phenyl or e) -benzyl.

5. A compound of claim 4 of formula II



II

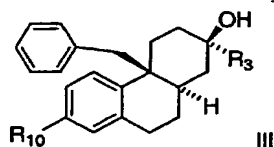
- an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;
- wherein R₁ is a) -(C₁-C₄)alkyl, b) -(C₂-C₄)alkenyl, c) -phenyl substituted with zero or one of the following: -OH, -NR₁₂R₁₃, -NR₁₂-C(O)-(C₁-C₄)alkyl, -CN, -Z-het, -O-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, -NR₁₂-Z-C(O)-NR₁₂R₁₃, -Z-NR₁₂-SO₂-R₁₃, -NR₁₂-SO₂-het, -O-C(O)-(C₁-C₄)alkyl or -O-SO₂-(C₁-C₄)alkyl; d) -O-phenyl substituted with 0 or 1 of the following: -Z-NR₁₂R₁₃ or -C(O)NR₁₂R₁₃, or e) -CH=CH-phenyl wherein phenyl is substituted with 0 or 1 of the following: -Z-NR₁₂R₁₃ or -C(O)NR₁₂R₁₃;
- Z for each occurrence is independently -(C₀-C₂)alkyl;
- R₁₀ is a) -CH(OH)(C₁-C₅)alkyl, b) -CN, c) -OH, d) -het, e) -C(O)-(C₁-C₄)alkyl, f) -C(O)-NR₁₂R₁₃, g) -C(O)-NH-Z-het, h) -O-(C₀-C₂)alkyl-het, i) -O-Z-C(O)-NR₁₂R₁₃, j) -O-Z-C(O)-NH-(C₀-C₃)alkyl-het or k) -O-Z-C(O)-NH-(C₀-C₃)alkyl-NR₁₂R₁₃;
- R₁₂ and R₁₃ are independently a) -H or b) -(C₁-C₄)alkyl;
- or R₁₂ and R₁₃ are taken together with N to form het.
6. A compound of claim 5 of formula II



II

- an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;
- wherein R₁ is a) -(C₂-C₄)alkyl, b) -CH₂-CH=CH₂ or c) -phenyl;
- R₂ is -OH;
- R₃ is a) -(C₁-C₆)alkyl substituted with 0 or 1 CF₃, b) -C≡C-CH₃, c) -C≡C-Cl, d) -C≡C-CF₃, e) -CH₂O(C₁-C₃)alkyl substituted with 0 or 1 CF₃, or f) -CF₃;
- R₁₀ is -OH or -CN.

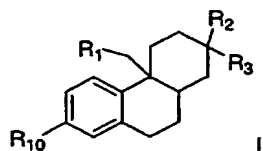
7. A compound of claim 6 of formula III



a prodrug thereof, or a pharmaceutically acceptable salt of said compound or prodrug;

wherein R_3 and R_{10} are as defined in claim 6.

5 8. A compound of claim 5 of formula II



an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

wherein R_1 is a) $-(C_2-C_4)alkyl$, b) $-CH_2-CH=CH_2$ or c) $-phenyl$;

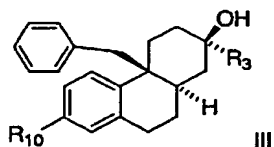
10 R_2 is $-OH$;

R_3 is a) $-(C_1-C_6)alkyl$ substituted with 0 or 1 CF_3 , b) $-C\equiv C-CH_3$, c) $-C\equiv C-Cl$, d) $-C\equiv C-CF_3$, e) $-CH_2O(C_1-C_3)alkyl$ substituted with 0 or 1 CF_3 , or f) $-CF_3$;

R_{10} is $-C(O)-NH-Z-het$ wherein het is selected from the group consisting of a) pyridinyl substituted with 0 or 1 methyl, b) pyrimidinyl, c) pyrazinyl, d) morpholinyl and e) oxadiazolyl;

15 Z is $-(C_0-C_2)alkyl$.

9. A compound of claim 8 of formula III



a prodrug thereof, or a pharmaceutically acceptable salt of said compound or prodrug;

wherein R_3 is a) $-(CH_2)_2-CF_3$, b) $-(CH_2)_2-CH_3$, c) $-CH_3$, d) $-C\equiv C-CH_3$, e) $-C\equiv C-Cl$ or f) $-CF_3$;

R_{10} is as defined in claim 8.

10. A compound of claim 9 selected from the group consisting of:

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(4-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(2-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(3-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-2-pyridinyl-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-pyrazinyl-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-3-pyridinyl-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-(2-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-(4-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-(3-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-2-pyridinyl-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-4-pyridinyl-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-N-3-pyridinyl-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-, (4bS,7S,8aR);

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4bS,7R,8aR);

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-4b-(phenylmethyl)-N-3-pyridinyl-, (4bS,7R,8aR)-; and

2-phenanthrenecarboxamide, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-N-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(trifluoromethyl)-, (4bS, 7R, 8aR)-;

or a prodrug thereof, or a pharmaceutically acceptable salt of said compound or prodrug.

11. A compound of claim 9 selected from the group consisting of:

a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(4-pyridinyl)$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2-pyridinyl)$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(3-pyridinyl)$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-(2-pyrazinyl)$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2-methyl-3-pyridinyl)$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2-methyl-3-pyridinyl)$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2-pyridinyl)$; or a pharmaceutically acceptable salt thereof;

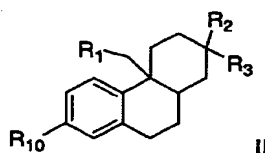
a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-C(O)-NH-CH_2-(2-methyl-3-pyridinyl)$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-C(O)-NH-CH_2-(2-methyl-3-pyridinyl)$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-C(O)-NH-(3-pyridinyl)$; or a pharmaceutically acceptable salt thereof; and

a compound of formula III wherein R_3 is $-CF_3$ and R_{10} is $-C(O)-NH-CH_2-(2-methyl-3-pyridinyl)$; or a pharmaceutically acceptable salt thereof.

12. A compound of claim 5 of formula II



an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

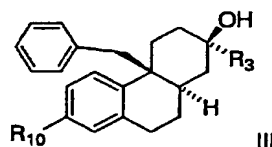
5 wherein R₁ is a) -(C₂-C₄)alkyl, b) -CH₂-CH=CH₂ or c) -phenyl;

R₂ is -OH;

R₃ is a) -(C₁-C₄)alkyl substituted with 0 or 1 CF₃, b) -C≡C-CH₃, c) -C≡C-Cl, d) -C≡C-CF₃, e) -CH₂O(C₁-C₃)alkyl substituted with 0 or 1 CF₃, or f) -CF₃;

R₁₀ is -O-(C₁-C₂)alkyl-het wherein het is selected from the group consisting of
10 a) pyridinyl substituted with 0 or 1 methyl, b) pyrimidinyl, c) pyrazinyl, d) morpholinyl and f) oxadiazolyl.

13. A compound of claim 12 of formula III



15 a prodrug thereof, or a pharmaceutically acceptable salt of said compound or prodrug;

wherein R₃ is a) -(CH₂)₂-CF₃, b) -(CH₂)₂-CH₃, c) -CH₃, d) -C≡C-CH₃, e) -C≡C-Cl or f) -CF₃;

R₁₀ is -O-(C₁-C₂)alkyl-het wherein het is selected from the group consisting of
20 a) 2-pyridinyl, b) 3-pyridinyl, c) 4-pyridinyl, d) 2-methyl-3-pyridinyl and e) pyrazinyl.

14. A compound of claim 13 selected from the group consisting of:

2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(3-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)];

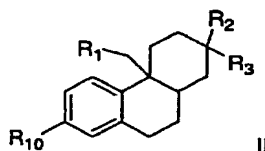
2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(4-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)];

2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-pyridinylmethoxy)-, [2*R*-(2α,4α,10aβ)];

- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(1-propynyl)-, [2*R*-(2 α ,4 α ,10 α)]-;
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α)]-;
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(2-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-;
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(3-pyridinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-;
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-4-pyridinyl)methoxy]-4a-(phenylmethyl)-2-propyl-, [2*R*-(2 α ,4 α ,10 α)]-;
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-propyl-7-(pyrazinylmethoxy)-, [2*R*-(2 α ,4 α ,10 α)]-;
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-(3,3,3-trifluoropropyl)-, [2*S*-(2 α ,4 α ,10 α)]-;
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(3,3,3-trifluoropropyl)-, [2*S*-(2 α ,4 α ,10 α)]-;
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(2-pyridinylmethoxy)-2-(3,3,3-trifluoropropyl)-, [2*S*-(2 α ,4 α ,10 α)]-; and
- 2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(trifluoromethyl)-, (2*R*,4*aS*,10*aR*)-;
- or a prodrug thereof, or a pharmaceutically acceptable salt of said compound or prodrug.
15. A compound of claim 13 selected from the group consisting of:
- a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-CH_2-(4\text{-pyridinyl})$; or a pharmaceutically acceptable salt thereof;
- a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-CH_2-(2\text{-pyridinyl})$; or a pharmaceutically acceptable salt thereof;
- a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-O-CH_2-(3\text{-pyridinyl})$; or a pharmaceutically acceptable salt thereof;
- a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-O-CH_2-(2\text{-methyl-3-pyridinyl})$; or a pharmaceutically acceptable salt thereof;
- a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-O-CH_2-(2\text{-pyridinyl})$; or a pharmaceutically acceptable salt thereof; and

a compound of formula III wherein R_3 is $-\text{CF}_3$ and R_{10} is $-\text{O}-\text{CH}_2-(2\text{-methyl-3-pyridinyl})$; or a pharmaceutically acceptable salt thereof.

16. A compound of claim 5 of formula II



5 an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug.

wherein R_1 is a) $-(\text{C}_2\text{-C}_4)\text{alkyl}$, b) $-\text{CH}_2\text{-CH=CH}_2$ or c) $-\text{phenyl}$;

R_2 is $-\text{OH}$;

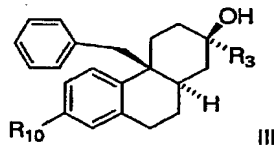
R_3 is a) $-(\text{C}_1\text{-C}_4)\text{alkyl}$ substituted with 0 or 1 CF_3 , b) $-\text{C}\equiv\text{C-CH}_3$, c) $-\text{C}\equiv\text{C-Cl}$, d) $-\text{C}\equiv\text{C-CF}_3$, e) $-\text{CH}_2\text{O}(\text{C}_1\text{-C}_3)\text{alkyl}$ substituted with 0 or 1 CF_3 , or f) $-\text{CF}_3$;

R_{10} is a) $-\text{O-Z-C(O)-NH-(C}_0\text{-C}_3)\text{alkyl-N}((\text{C}_1\text{-C}_2)\text{alkyl})_2$, b) $-\text{O-Z-C(O)-NR}_{12}\text{R}_{13}$, or c) $-\text{O-Z-C(O)-NH-(C}_0\text{-C}_3)\text{alkyl-het}$ wherein het is selected from the group consisting of 1) pyridinyl substituted with 0 or 1 methyl, 2) pyrimidinyl, 3) pyrazinyl, 4) morpholinyl, 5) pyrrolidinyl, 6) imidazolyl and 7) oxadiazolyl;

R_{12} and R_{13} are independently a) $-\text{H}$ or b) $-(\text{C}_1\text{-C}_2)\text{alkyl}$; or R_{12} and R_{13} taken together with N to form pyrrolidinyl;

Z is $-(\text{C}_0\text{-C}_1)\text{alkyl}$.

17. A compound of claim 16 of formula III



20 a prodrug thereof, or a pharmaceutically acceptable salt of said compound or prodrug;

wherein R_3 is a) $-(\text{CH}_2)_2\text{CF}_3$, b) $-(\text{CH}_2)_2\text{-CH}_3$, c) $-\text{CH}_3$, d) $-\text{C}\equiv\text{C-CH}_3$, e) $-\text{C}\equiv\text{C-Cl}$ or f) $-\text{CF}_3$;

R_{10} is a) $-\text{O-C(O)-NH-(C}_0\text{-C}_3)\text{alkyl-N}((\text{C}_1\text{-C}_2)\text{alkyl})_2$, b) $-\text{O-C(O)-N(CH}_3)_2$, c) $-\text{O-C(O)-(1-pyrrolidinyl)}$ or d) $-\text{O-C(O)-NH-(C}_0\text{-C}_3)\text{alkyl-het}$ wherein het is selected from the group consisting of 1) 2-pyridinyl, 2) 3-pyridinyl, 3) 4-pyridinyl, 4) 2-methyl-3-pyridinyl, 5) pyrazinyl, 6) morpholinyl, 7) pyrrolidinyl and 8) imidazolyl.

18. A compound of claim 17 selected from the group consisting of:

carbamic acid, dimethyl-, 7-(chloroethynyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-2-phenanthrenyl ester, (4bS,8aR)-;

1-pyrrolidinecarboxylic acid, 7-(chloroethynyl)-4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-2-phenanthrenyl ester, (4bS,8aR)-;

carbamic acid, [2-(1-pyrrolidinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-

hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, monohydrochloride, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, [2-(4-morpholinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-

hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, [3-(1H-imidazol-1-yl)propyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-

hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, [2-(dimethylamino)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-

hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, [3-(1-pyrrolidinyl)propyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-

hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, [2-(3-pyridinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-

4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, (2-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-

(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, [2-(2-pyridinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-

4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, (4-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-

(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

carbamic acid, (3-pyridinylmethyl)-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-

(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-; and

carbamic acid, [2-(4-pyridinyl)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-

4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)]-;

or a prodrug thereof, or a pharmaceutically acceptable salt of said compound

or prodrug.

19. A compound of claim 17 selected from the group consisting of

a compound of formula III wherein R₃ is -C \equiv C-CH₃ and R₁₀ is

-O-C(O)-NH-(CH₂)₂-(1-pyrrolidinyl); or a pharmaceutically acceptable salt thereof;

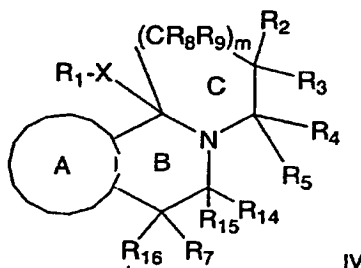
a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-C(O)-NH-(CH_2)_2-N(CH_3)_2$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-C(O)-NH-CH_2-2$ -pyridyl; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-C(O)-NH-CH_2-4$ -pyridyl; or a pharmaceutically acceptable salt thereof; and

a compound of formula III wherein R_3 is $-C\equiv C-CH_3$ and R_{10} is $-O-C(O)-NH-CH_2-3$ -pyridyl; or a pharmaceutically acceptable salt thereof.

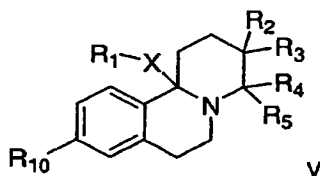
20. A compound of claim 1 of formula IV



an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

wherein R_8 is $-H$; R_9 is $-H$; m is 2; R_7 is $-H$; R_{14} is $-H$; R_{15} is $-H$; R_{16} is $-H$; and the A-ring is the moiety of formula A-1a.

21. A compound of claim 20 of formula V



an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

wherein X is $-CH_2-$;

R_1 is a) $-(C_1-C_4)$ alkyl, b) $-(C_2-C_4)$ alkenyl, c) $-phenyl$ substituted with 0 or 1 of the following: $-OH$, $-NR_{12}R_{13}$, $-NR_{12}-C(O)-(C_1-C_4)$ alkyl, $-CN$, $-Z$ -het,

-O-(C₁-C₃)alkyl-C(O)-NR₁₂R₁₃, -NR₁₂-Z-C(O)-NR₁₂R₁₃, -Z-NR₁₂-SO₂-R₁₃,
 -NR₁₂-SO₂-het, -O-C(O)-(C₁-C₄)alkyl or -O-SO₂-(C₁-C₄)alkyl; d) -O-phenyl substituted
 with 0 or 1 of the following: -Z-NR₁₂R₁₃ or -C(O)NR₁₂R₁₃; or e) -CH=CH-phenyl
 wherein phenyl is substituted with 0 or 1 of the following: -Z-NR₁₂R₁₃ or -C(O)NR₁₂R₁₃;

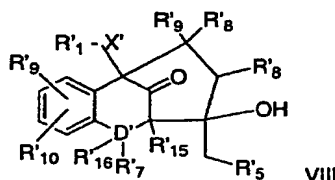
5 Z is for each occurrence independently -(C₀-C₂)alkyl;

R₄ and R₅ are each hydrogen or are taken together to form =O;

15 R₁₀ is a) -CH(OH)(C₁-C₅)alkyl, b) -CN, c) -OH, d) -het, e) -C(O)-(C₁-C₄)alkyl, f)
 -C(O)-NR₁₂R₁₃, g) -C(O)-NH-Z-het, h) -O-(C₀-C₃)alkyl-het, i) -O-Z-C(O)-NR₁₂R₁₃, j)
 -O-Z-C(O)-NH-(C₀-C₃)alkyl-het or k) -O-(C₀-C₃)alkyl-phenyl;

10 R₁₂ and R₁₃ for each occurrence are independently a) -H or b) -(C₁-C₄)alkyl.

22. A compound of formula VIII



or an isomer thereof;

wherein D' is C;

15 X' is -CH₂-;

R'1 is phenyl substituted with 0 to 2 R'_x;

35 R'5, R'7, R'8, R'9, R'15 and R'16 for each occurrence are independently a) -H, b)
 -O-(C₁-C₆)alkyl, c) -(C₁-C₆)alkyl or d) halo;

20 R'10 is a) -halo, b) -CN, c) -OH, d) -C(O)-NR'12R'13, e) -C(O)-NR'12-Z'-het
 wherein het is substituted with 0 or 1 R'_x, f) -C(O)-NR'12-Z'-aryl wherein aryl is
 substituted with 0 or 1 R'_x, g) -O-(C₀-C₆)alkyl-het wherein het is substituted with 0 or 1
 R'_x, or h) -O-(C₀-C₆)alkyl-aryl wherein aryl is substituted with 0 or 1 R'_x;

40 Z' is a) -(C₀-C₆)alkyl, b) -(C₂-C₆)alkenyl, or c) -(C₂-C₆)alkynyl;

R'_x is a) -halo, b) -OH, c) -(C₁-C₆)alkyl, d) -CN, e) -CF₃, f)

25 -(C₀-C₆)alkyl-NR'12R'13, g) -C(O)-NR'12R'13, h) -NR'12-SO₂R'13, i) -NR'12-C(O)-R'13, j)
 -SO₂R'12 or k) -SO₂-NR'12R'13;

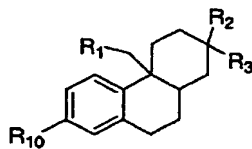
45 R'12 and R'13 for each occurrence are each independently a) -H or b)

-(C₁-C₆)alkyl;

aryl is phenyl;

het is a 5-, 6- or 7-membered saturated, partially saturated or unsaturated ring containing from one (1) to three (3) heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur.

23. A compound of claim 3 of formula II



an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

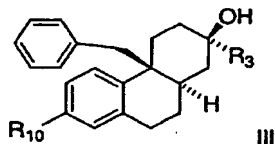
wherein R₁ is -phenyl;

R₂ is -OH;

R₃ is a) -(C₁-C₆)alkyl substituted with 0 or 1 CF₃, b) -C≡C-CH₃, c) -C≡C-Cl, d) -C≡C-CF₃, e) -CH₂O(C₁-C₃)alkyl substituted with 0 or 1 CF₃, or f) -CF₃;

R₁₀ is -OH, -CN, -C(O)OH or -C(O)O(C₁-C₆)alkyl.

24. A compound of claim 23 of formula III



a prodrug thereof, or a pharmaceutically acceptable salt of said compound or prodrug;

wherein R₃ is a) -(CH₂)₂-CF₃, b) -(CH₂)₂-CH₃, c) -CH₃, d) -C≡C-CH₃, e) -C≡C-Cl or f) -CF₃;

R₁₀ is as defined in claim 23.

25. A compound of claim 24 selected from the group consisting of:

a compound of formula III wherein R₃ is -C≡C-CH₃ and R₁₀ is -OH; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R₃ is -C≡C-CH₃ and R₁₀ is -CN; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R₃ is -C≡C-CH₃ and R₁₀ is -COOH; or a pharmaceutically acceptable salt thereof;

5 a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof;

10 a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof;

5 a compound of formula III wherein R_3 is $-(CH_2)_2-CH_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof;

15 a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof;

10 a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof;

20 a compound of formula III wherein R_3 is $-(CH_2)_2-CF_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof;

25 15 a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-CH_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof;

30 20 a compound of formula III wherein R_3 is $-CF_3$ and R_{10} is $-OH$; or a pharmaceutically acceptable salt thereof;

a compound of formula III wherein R_3 is $-CF_3$ and R_{10} is $-CN$; or a pharmaceutically acceptable salt thereof; and

35 a compound of formula III wherein R_3 is $-CF_3$ and R_{10} is $-COOH$; or a pharmaceutically acceptable salt thereof.

25 26. Use of a compound of claim 1, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug, for the manufacture of a medicament for the treatment of a condition selected from the group consisting of obesity, diabetes, anxiety, depression, neurodegeneration or an inflammatory disease in a mammal.

40 30 27. The use of claim 26 wherein the condition is obesity.

45 28. The use of claim 27 which further comprises administering a β_3 agonist, a thyromimetic agent, an eating behavior modifying agent or a NPY antagonist.

29. The use of claim 28 wherein the second compound is orlistat or sibutramine.

50 30. The use of claim 26 wherein the condition is diabetes.

5
10 31. The use of claim 30 which further comprises administering an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin, troglitazone sulfonylureas, glipizide, glyburide, or chlorpropamide.

5 32. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug; and a pharmaceutically acceptable carrier, vehicle or diluent.

15 33. A pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising:

10 a first compound, said first compound being a compound of claim 1, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

20 a second compound, said second compound being a β_3 agonist, a thyromimetic agent, an eating behavior modifying agent or a NPY antagonist; and

25 15 a pharmaceutical carrier, vehicle or diluent.

34. A kit comprising:

30 a) a first compound, said first compound being a compound of claim 1, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug and a pharmaceutically acceptable carrier, vehicle or diluent in a first unit dosage form;

35 b) a second compound, said second compound being a β_3 agonist, a thyromimetic agent, an eating behavior modifying agent or a NPY antagonist; and a pharmaceutically acceptable carrier, vehicle or diluent in a second unit dosage form; and

25 c) a container for containing said first and second dosage forms; wherein the amounts of said first and second compounds result in a therapeutic effect.

40 35. Use of a compound of claim 1, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug, for the manufacture of a medicament for inducing weight loss in a mammal.

45 36. A pharmaceutical combination composition comprising: a therapeutically effective amount of a composition comprising:

50 a first compound, said first compound being a compound of claim 1, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

a second compound, said second compound being an aldose reductase inhibitor, a glycogen phosphorylase inhibitor, a sorbitol dehydrogenase inhibitor, insulin, troglitazone, sulfonylureas, glipizide, glyburide, or chlorpropamide; and a pharmaceutical carrier, vehicle or diluent.

37. Use of a glucocorticoid receptor modulator and a glucocorticoid receptor agonist for the manufacture of a medicament for the treatment of an inflammatory disease in a mammal and for reducing the undesirable side effects of said treatment.

38. The use of claim 37 wherein the inflammatory disease is selected from the group consisting of arthritis, asthma, rhinitis and immunomodulation.

39. The use of claim 37 wherein the glucocorticoid receptor modulator is a compound of claim 1, an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug;

40. The use of claim 37 wherein the glucocorticoid receptor agonist is a compound selected from the group consisting of prednisone, prednylidene, prednisolone, cortisone, dexamethasone and hydrocortisone.

41. The use of claim 39 wherein the glucocorticoid receptor modulator is a compound selected from the group consisting of:

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(4-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(2-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-(3-pyridinylmethyl)-, [4bS-(4b α ,7 α ,8a β)];

carbamic acid, [2-(dimethylamino)ethyl]-, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-2-phenanthrenyl ester, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-N-pyrazinyl-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(4-pyridinylmethoxy)-, [2R-(2 α ,4a α ,10a β)];

2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-2-(1-propynyl)-7-(2-pyridinylmethoxy)-, [2R-(2 α ,4a α ,10a β)];

2-phenanthrenecarbonitrile, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-(1-propynyl)-, [4bS-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(1-propynyl)-, [4b*S*-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-propyl-, [4b*S*-(4b α ,7 α ,8a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-4b-(phenylmethyl)-7-propyl-*N*-(2-pyridinylmethyl)-, [4b*S*-(4b α ,7 α ,8a β)];

2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-4a-(phenylmethyl)-7-(3-pyridinylmethoxy)-2-(3,3,3-trifluoropropyl)-, [2*S*-(2 α ,4a α ,10a β)];

2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(3,3,3-trifluoropropyl)-, [2*S*-(2 α ,4a α ,10a β)];

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(3,3,3-trifluoropropyl)-, (4b*S*,7*S*,8a*R*);

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-, (4b*S*,7*R*,8a*R*);

2-phenanthrenecarboxamide, 4b,5,6,7,8,8a,9,10-octahydro-7-hydroxy-7-methyl-4b-(phenylmethyl)-*N*-3-pyridinyl-, (4b*S*,7*R*,8a*R*);

2-phenanthrenol, 1,2,3,4,4a,9,10,10a-octahydro-7-[(2-methyl-3-pyridinyl)methoxy]-4a-(phenylmethyl)-2-(trifluoromethyl)-, (2*R*,4a*S*,10a*R*); and

2-phenanthrenecarboxamide, 4b, 5, 6, 7, 8, 8a, 9, 10-octahydro-7-hydroxy-*N*-[(2-methyl-3-pyridinyl)methyl]-4b-(phenylmethyl)-7-(trifluoromethyl)-, (4b*S*, 7*R*, 8a*R*);

or an isomer thereof, a prodrug of said compound or isomer, or a pharmaceutically acceptable salt of said compound, isomer or prodrug.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/IB 00/00366

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C35/42 A61K31/05 A61K31/122 A61K31/325 A61K31/4402
A61K31/4406 A61K31/4409 C07C49/675 C07C271/44 C07D213/40
C07D213/30 C07D213/75 C07D241/18 C07D241/20 C07D295/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 084, no. 19, 10 May 1976 (1976-05-10) Columbus, Ohio, US; abstract no. 135496, KIGASAWA K ET AL: "1,2-Cycloalkanoisoquinolines" XP002140926 see the abstract; in particular, the compounds of the formulae I and II wherein R = Ph and n = 2 or 3 abstract -& JP 50 111098 - (GRELAN PHARMACEUTICAL CO., LTD.; JAPAN) --- -/-	1,2,20

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

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E earlier document but published on or after the international filing date
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O document referring to an oral disclosure, use, exhibition or other means
P document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
S document member of the same patent family

Date of the actual completion of the international search

23 June 2000

Date of mailing of the international search report

24.08.00

Name and mailing address of the ISA
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 00/00366A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 31702 A (GROEN MARINUS BERNARD ;AKZO NOBEL NV (NL); GEBHARD RONALD (NL)) 23 July 1998 (1998-07-23) cited in the application the whole document	1-36, 39, 41
A	EP 0 188 396 A (ROUSSEL UCLAF) 23 July 1986 (1986-07-23) cited in the application the whole document	1-36, 39, 41

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

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O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

A document member of the same patent family

Date of the actual completion of the international search

23 June 2000

Date of mailing of the international search report

24.08.00

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F1nk, D

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 00/00366

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-36, 39, 41

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

1. Claims: 1-36,39,41

the compounds of the present formula I (cf. the present claims 1-21 and 23-25), the intermediate compounds of the present formula VIII (cf. the present claim 22), the use of the compounds of the present claim 1 in the manufacture of a medicament for the treatment of obesity, diabetes, anxiety, depression, neurodegeneration or an inflammatory disease and of a medicament for inducing weight loss (cf. the present claims 26-31, 35, 39 and 41), a pharmaceutical composition comprising a compound of the present claim 1 (cf. the present claims 32, 33 and 36), and a kit comprising a compound of the present claim 1 (cf. the present claim 34);

2. Claims: 37,38,40

the use of a known glucocorticoid receptor modulator and a known glucocorticoid receptor agonist for the manufacture of a medicament for the treatment of an inflammatory disease (and for reducing the undesirable side effects of said treatment) (cf. the present claims 37, 38 and 40);

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/IB 00/00366

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 50111098	-	NONE	
WO 9831702	A	23-07-1998	
		AU 6293598 A	07-08-1998
		CN 1248262 T	22-03-2000
		EP 0973792 A	26-01-2000
		NO 993459 A	07-09-1999
		PL 334518 A	28-02-2000
		US 6072068 A	06-06-2000
		ZA 9800084 A	08-07-1998
EP 0188396	A	23-07-1986	
		FR 2576025 A	18-07-1986
		AT 45955 T	15-09-1989
		AU 582618 B	06-04-1989
		AU 5228386 A	17-07-1986
		CA 1266466 A	06-03-1990
		DE 3665306 D	05-10-1989
		DK 13286 A	15-07-1986
		ES 550822 D	16-01-1988
		ES 8801509 A	16-03-1988
		HU 41047 A, B	30-03-1987
		IE 59010 B	03-12-1993
		JP 2052483 C	10-05-1996
		JP 7072193 B	02-08-1995
		JP 61168029 A	29-07-1986
		JP 2687209 B	08-12-1997
		JP 7316185 A	05-12-1995
		KR 9305993 B	01-07-1993
		US 4753932 A	28-06-1988
		ZA 8600146 A	25-03-1987

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